SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Implantable Middle Ear Hearing Device
Device Trade Name:	Esteem® ,consisting of: Sound Processor Model 2001 Sensor Model 7002 Driver Model 7502 Esteem Programmer Model 6001 Personal Programmer Model 8001 Intraoperative System Analyzer Model 3001 Accessories
Applicant's Name and Address:	Envoy Medical Corporation 5000 Township Parkway St. Paul, MN 55110
Date of Panel Recommendation:	December 18, 2009
Premarket Application (PMA) Number:	P090018
Date of FDA Notice of Approval:	March 17, 2010
Expedited:	Granted expedited review status on August 27, 2009 because the Esteem® represents a breakthrough technology which provides an alternative to non-implantable and partially implantable hearing aid technology.

II. INDICATIONS FOR USE

The Esteem is intended to alleviate hearing loss in patients by replicating the ossicular chain and providing additional gain. The Esteem is indicated for patients with hearing loss that meet the following criteria:

- 18 years of age or older
- Stable bilateral sensorineural hearing loss
- Moderate to severe sensorineural hearing loss defined by Pure Tone Average (PTA)
- Unaided speech discrimination test score greater than or equal to 40%
- Normally functioning Eustachian tube
- Normal middle ear anatomy
- Normal tympanic membrane
- Adequate space for Esteem implant determined via high resolution CT scan
- Minimum 30 days of experience with appropriately fit hearing aids.

III. CONTRAINDICATIONS

Esteem® is contraindicated under the following conditions:

- History of post-adolescent chronic middle ear infections, inner ear disorders or recurring vertigo requiring treatment, disorders such as mastoiditis, Hydrops or Meniere's syndrome or disease
- Known history of fluctuating air conduction and/or bone conduction hearing loss over the past one year period of 15 dB in either direction at 2 or more frequencies (from 500 to 4000 Hz)
- History of otitis externa or eczema for the outer ear canal
- Cholesteatoma or destructive middle ear disease
- Retrocochlear or central auditory disorders
- Disabling tinnitus, defined as tinnitus which requires treatment
- History of keloid formation
- Hypersensitivity to silicone rubber, polyurethane, stainless steel, titanium and/or gold
- A pre-existing medical condition or undergoing a treatment that may affect healing process
- During pregnancy

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Esteem® labeling.

V. DEVICE DESCRIPTION

The Esteem is a totally implantable middle ear hearing device. The Esteem consists of three implantable components, the Sound Processor, the Sensor and the Driver, and external instruments for interrogating, testing and programming the Esteem. Specifically, the Esteem includes the Model 2001 Sound Processor, Sensor Model 7002, Driver Model 7502, Esteem Programmer Model 6001 with Esteem Programmer Software and Wand, Personal Programmer Model 8001, Intraoperative System Analyzer Model 3001, and accessories.

Implantable Components:
1. Sensor: The piezoelectric Sensor tip is attached to the incus bone. The Sensor senses vibrations from the tympanic membrane and malleus/incus and converts these mechanical vibrations into electrical signals that are sent to the Sound Processor (Fig. 1).

2. Sound Processor: The Sound Processor, which is implanted in the temporal bone and connected to the Sensor and Driver via leads, receives the electrical signal from the Sensor, amplifies and filters the signal to compensate for the patient's hearing loss profile. The enhanced signal is then sent to the Driver (Fig. 1).

3. Driver: The piezoelectric Driver tip is attached to the stapes/incus bone. The Driver converts the enhanced electrical signal received from the Sound Processor back to

mechanical energy, i. e. vibrations. The vibrations are transferred to the stapes and delivered as sound waves in the cochlea (Fig. 1).

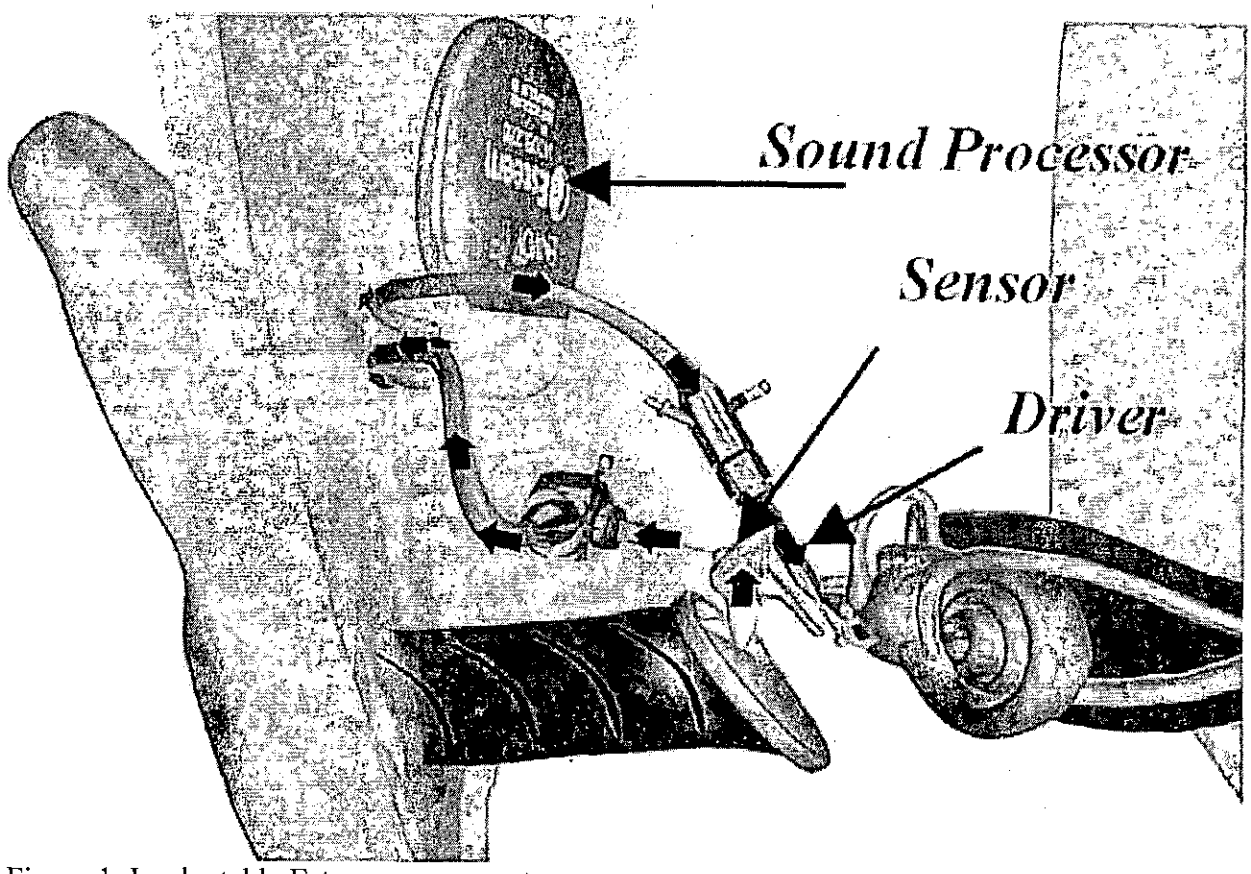


Figure 1. Implantable Esteem components.

External Instruments:
1. Esteem Programmer: This portable computer with the Esteem Programmer Software and a bi-directional telemetry wand is used to interrogate the implanted Sound Processor and to program it to a custom prescription for each patient.

2. Personal Programmer: This remote control device is used by the patient to adjust the volume and select pre-programmed settings in the Sound Processor.

3. Intraoperative System Analyzer: The ISA is a test system, consisting of a computer, software, Patient Interface Device and cables, used to verify the function of the implantable components during the implant procedure.

Accessories:
1. Unique Accessories: Several unique accessories are used during the implantation of the Esteem. The Glasscock Stabilizer is a sterile temporary retainer used to position and stabilize the Sensor and Driver during implant. The Replica Sound Processor is a tool used by the implanting physician to assess the space and placement requirements for the implantable Sound Processor. EnvoyCem is cement used to bond the Sensor and Driver

tips to the ossicular chain. MedCem is bone cement used to anchor the Sensor and Driver to the mastoid floor during implant.

2. Standard Surgical Accessories: The surgical team may use several commercially available accessories that are either FDA cleared or exempt during the implant of the Esteem. These include bone screws, screwdriver, pliers, pick, syringes and sterilization tray.

Please refer to the Operator's Manual for additional details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of hearing loss. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Alternate practices and procedures include acoustic hearing aids and semi-implantable middle ear hearing devices. Hearing aids can be worn in a variety of configurations, including behind the ear, in the ear, in the canal or completely in the ear canal. Semi-implantable middle ear hearing devices typically consist of a middle ear implant and an external sound processing unit worn in and/or behind the ear.

VII. MARKETING HISTORY

The Esteem received CE Mark certification approval May 3, 2006. Since market introduction, Envoy Medical has distributed approximately 85-100 Esteem devices throughout the European Union and Switzerland. In addition, approximately 20 Esteem devices have been distributed in India, Iran and Brazil since introduction in early 2008. The Esteem was also granted a Canadian License in March 2008 but no Esteem devices have been distributed to date. The Esteem has not been withdrawn from any market for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Surgery of the middle ear to implant the Esteem involves manipulation and dissection of the ossicular chain (incus, malleus, and stapes) and exposes the inner ear to the risk of surgical trauma. Serious complications may occur during or after the surgery that may include, but are not limited to:

- loss in residual hearing due to surgical trauma
- device displacement after surgery,
- tissue buildup causing feedback or limited benefit
- device failure

- infection after surgery.

Additional complications include:

- swelling
- numbness and discomfort around the ear after surgery
- facial paralysis/paresis
- taste disturbance
- numbness of the tongue and face

For the specific adverse events that occurred in the clinical studies, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Biocompatibility

Biocompatibility testing was conducted on all body contacting materials prepared to represent the finished device, as it would be implanted in the patient. All toxicity endpoints recommended for evaluation by ISO 10993-1: 2003 Biological Evaluation of Medical and Dental Materials and Devices, Part 1: Guidance on Selection of Tests and FDA Blue Book memorandum G95-1 were addressed. Tests conducted fall into the ISO guidance category for permanent (>30 days) implantable, bone and tissue contacting devices. In addition, all materials used in the implant accessory devices were subjected to tests in accordance to the ISO Guidance category for implant devices contacting tissue/bone for a limited (<24 hours) duration. All results for cytotoxicity, sensitization, implantation, chronic/acute toxicity and carcinogenicity were acceptable.

Implanted System Assemblies/Materials - ***Permanent Exposure (>30 Days)***

Test	Test Method	Results
Cytotoxicity – L929 MEM Elution	According to ISO 10993-5; The "in-vitro" biological reactivity of the L929 mouse fibroblast cell culture is determined in response to an extract of the test material. The cells are allowed to grow to sub-confluency in tissue culture plates. An extract of the test material is prepared in Minimum Essential Media (MEM), which is transferred onto the cell layer. The plates are incubated for forty-eight hours at 37°C in a 5% Co_2 incubator, and scored for reactivity at twenty-four and forty-eight hours.	The test article is considered non-cytotoxic and meets the requirements of ISO 10993-5 guidelines.

Test	Test Method	Results
Sensitization - Klingman Maximization	According to ISO 10993-10; The test article will be exposed through test article extracts. Extracts of the test material are prepared in a (cotton seed oil) solution. The test begins with intradermal injections of Freund's Complete Adjuvant (FCA) and the test article. Seven days later the injection sites are covered with the test article or extract for a period of forty-eight hours. Fourteen days later a virgin site is challenged with a topical application of the test article or extract and scored at forty-eight hours.	Grade 1 reaction. A Grade 1 sensitization rate is not considered significant and the test article meets the requirements of the ISO 10993-10 guidelines.
Irritation - Intracutaneous Injection	According to ISO 10993-10; The test article will be exposed through test article extracts. Extracts of the test material are prepared in a (cotton seed oil) solution. A minimum of two rabbits are injected intracutaneously with the test article and control materials. The injected sites are examined over a seventy-two hour period for evidence of tissue reaction such as erythema, edema, and necrosis. Observations are scored according to the Classification System for Scoring Skin Reactions (Draize scale).	The test article is considered a negligible irritant and meets the requirements of ISO 10993-10 guidelines.
Acute Systemic Toxicity-Systemic Injection Test	According to ISO 10993-10; Mice are injected systemically with extracts of the test article in standard solutions (normal saline and cottonseed oil). The animals are observed for signs of toxicity immediately after injection and at 4, 24, 48 and 72 hours post injection. The requirements of the test are met if none of the animals treated with the test article extract have a significantly greater adverse reaction the animals treated with the vehicle control.	This test found no systemic toxicity and meets the requirements of ISO 10993-11 guidelines.
Genotoxicity - Bacterial Reverse Mutation Assay	According to ISO 10993-3; The in-vitro assay is performed using Salmonella typhimurium to detect reverse mutations in histidine gene in a histidine-requiring strain to produce histidine-independence. Bacteria are plated onto histidine free medium and the plate is exposed to the test article extract. The plate is incubated and observed for growth after exposure. If the extract is showing mutagenic properties, reverse-mutated bacteria will now be able to grow on histidine free medium. The number of colonies is directly proportional to the mutagen potency.	The test article is considered non-mutagenic and meets the requirements of ISO 10993-3 guidelines.

Test	Test Method	Results
Genotoxicity - Mouse Lymphoma Assay	According to ISO 10993-3; The test article is administered in vitro, through a solvent compatible with the test system. At least 200 metaphase cells will be analyzed for each test article extract and negative control.	The test article is considered non-mutagenic and meets the requirements of ISO 10993-3 guidelines.
Genotoxicity – DNA-Effects-Rodent Micronucleus Assay	According to ISO 10993-3; The in-vivo assay is performed by exposing the bone marrow of mice to the test article extract. The bone marrow is collected at predetermined harvest times (24 and 48 hours after treatment). Bone marrow smears are prepared and analyzed for the presence of micronuclei.	The test article is considered non-mutagenic and meets the requirements of ISO 10993-3 guidelines.
Implantation - Short and Long Term	According to ISO 10993-6; Test and control material is implanted into the paravertebral muscle (for Intramuscular implants) of each of three rabbits. At the end of the observation period, the area of the tissue surrounding the center position of each implant strip will be examined macroscopically. Following gross observations, a veterinary pathologist will process the implanted sites for histopathologic evaluation. Inflammation, fibrosis, hemorrhagic and necrosis are evaluated on a scale and compared to the control article sites. Short Term = 2 weeks Long Term = 12 weeks	The test article is considered a non-irritant and meets the requirements of ISO 10993-6 guidelines.

Tissue/Bone Contacting Accessories/Materials - **Limited Exposure (<24 hours)**

Test	Test Method	Results
Cytotoxicity – L929 MEM Elution	According to ISO 10993-5; The "in-vitro" biological reactivity of the L929 mouse fibroblast cell culture is determined in response to an extract of the test material. The cells are allowed to grow to sub-confluency in tissue culture plates. An extract of the test material is prepared in Minimum Essential Media (MEM), which is transferred onto the cell layer. The plates are incubated for forty-eight hours at 37°C in a 5% Co_2 incubator, and scored for reactivity at twenty-four and forty-eight hours.	The test article is considered non-cytotoxic and meets the requirements of ISO 10993-5 guidelines.

Test	Test Method	Results
Sensitization - Klingman Maximization	According to ISO 10993-10; The test article will be exposed through test article extracts. Extracts of the test material are prepared in a (cotton seed oil) solution. The test begins with intradermal injections of Freund's Complete Adjuvant (FCA) and the test article. Seven days later the injection sites are covered with the test article or extract for a period of forty-eight hours. Fourteen days later a virgin site is challenged with a topical application of the test article or extract and scored at forty-eight hours.	Grade 1 reaction. A Grade 1 sensitization rate is not considered significant and the test article meets the requirements of the ISO 10993-10 guidelines.
Irritation - Intracutaneous Reactivity	According to ISO 10993-10; The test article will be exposed through test article extracts. Extracts of the test material are prepared in a (cotton seed oil) solution. A minimum of two rabbits are injected intracutaneously with the test article and control materials. The injected sites are examined over a seventy-two hour period for evidence of tissue reaction such as erythema, edema, and necrosis. Observations are scored according to the Classification System for Scoring Skin Reactions (Draize scale).	The test article is considered a negligible irritant and meets the requirements of ISO 10993-10 guidelines
Acute Systemic Toxicity-Systemic Injection Test	According to ISO 10993-10; Mice are injected systemically with extracts of the test article in standard solutions (normal saline and cottonseed oil). The animals are observed for signs of toxicity immediately after injection and at 4, 24, 48 and 72 hours post injection. The requirements of the test are met if none of the animals treated with the test article extract have a significantly greater adverse reaction the animals treated with the vehicle control.	This test found no systemic toxicity and meets the requirements of ISO 10993-11 guidelines.

Electrical Testing

Extensive testing was conducted on the Esteem to verify the design criteria and device performance with respect to the electrical properties and specifications in support of its safety and effectiveness.

1. Implantable Components:

Test	Requirement	Results
Lead Continuity Resistance	Non-hermetic electrical connections between implanted system components shall have a combined series resistance of less than 50 ohms.	Passed
Lead Isolation Resistance	Non-hermetic electrical connections between implanted system components shall maintain a minimum isolation resistance of at least 5 mega-ohms.	Passed
Harmonic Distortion	The device shall exhibit less than 10% harmonic distortion for nominal signals as tested per ANSI S3.22 1996	Passed
Input Noise	Total input-referred rms noise shall be less than 25 dB SPL over the range 200 Hz to 8000 Hz	Passed
Volume Control	Volume shall be programmable over at least a 21 dB range.	Passed
Programmable Output Limiting	Maximum output level shall be programmable over at least a 12 dB range.	Passed
Confirmation Tone	The implanted system shall output a confirmation tone after a valid communication from the external programmer.	Passed
Implanted Battery Longevity	The implanted battery life shall be at least 5.0 years of typical operation, including a 1.0 year shelf life.	Passed
BERI to EOL Operation	The device shall continue to function for 14 days of typical operation after initial Battery Elective Replacement Indicator (BERI)	Passed
Heat Generation	In normal operation or any single fault condition, no outer surface of the device shall be more than 2°C above surrounding tissue temperature at 37°C.	Passed
Implant Electromagnetic Sensitivity	In electromagnetic environments (EN 60601-1-2 or ANSI/AAMI PC69) the implanted components of the system shall not generate an output exceeding an equivalent input audio level of 85 dB SPL at 1kHz.	Passed
Implant Electromagnetic Data Integrity	In electromagnetic environments (EN 60601-1-2 or ANSI/AAMI PC69) the implanted components of the system shall maintain internally stored data.	Passed
Electrostatic Discharge	When subject to ESD exposure according to IEC 60601-1-2 Section 36.202.2, the implanted device shall exhibit no loss of internally stored data and no operational change.	Passed
Identification	The implanted device shall store a unique serial number that can be interrogated by telemetry.	Passed

2. External Components:

Test	Requirement	Results
Electrostatic Discharge	After ESD exposure according to IEC 60601-1-2 and EN 45502-1, external components of the system will operate within normal limits.	Passed
Radiated Emissions	External components of the system shall not transmit electromagnetic fields at levels above 30.0 dBuV/m in the range 30 – 230 MHz or above 37.0 dBuV/m in the range 230 – 1000 MHz.	Passed
Radiated Immunity	The system shall provide means for ensuring integrity of transmissions between implant and external components in a 3 V/m electromagnetic environment over the range 80 MHz to 2.7 GHz.	Passed

Mechanical Testing

Extensive testing was conducted on the Esteem to verify the design criteria and device performance with respect to the mechanical properties and specifications in support of its safety and effectiveness.

1. Implantable Components:

Test	Requirement	Results
Lead Flex	Transducer leads to maintain continuity of 10 Ω or less following 82,000 flexural cycles at ±45° deflection.	Passed
Hermeticity validation	Transducer & Sound Processors to be Hermetic to 1x10-8 atm cm3/s when tested per MIL-STD-883 and Validated Internal Test Methods	Passed
Implantable components Shock and vibration	Implantable components in final packaging of to endure multiple drop sequences, implanted devices without packaging to endure vibration regimens per: EN 45502-1; 23.2.	Passed
Packaging testing	Final Packaging to Endure simulated distribution-shipping conditions per ASTM D4169.	Passed
Implantable components Operating and Storage Temperature	Implantable components to endure Storage Conditions of 0°C to 50°C and absolute humidity < 20 g/m3, and demonstrate operation in 35°C to 40°C with 30% to 100% Relative Humidity per EN 45502-1.	Passed

2. External Components:

Test	Requirement	Results
Personal Programmer Shock & Vibration Testing	Personal Programmer to endure multiple drop sequences and vibration regimens 5-150 Hz 0.1 g2/Hz EN 45502-1; 23.1.	Passed

Test	Requirement	Results
Personal Programmer Operating and Storage Conditions	Personal Programmer to endure Storage Conditions of -20°C to 60°C with and Relative Humidity from 15% to 95%, and demonstrate operation in 10°C to 30°C and Relative Humidity from 15% to 95%, as well as Absolute pressures spanning 700 hPa and 1060 hPa. per EN 45502-1.	Passed
Esteem Programmer Operating Conditions	Esteem Programmer to demonstrate operation in 10°C to 30°C with Relative Humidity of 20% to 80%, non-condensing.	Passed
Personal Programmer Spill-proof	Personal Programmer to demonstrate ability to endure a liquid spill, a drying sequence, and a 1 minute 2500 VDC over-voltage exposure, and remain functional.	Passed

Life Testing

A series of *in vitro* life test studies were conducted on the Sensor and the Driver transducers, the Sound Processor, and the System as a whole under accelerated conditions to evaluate potential failure mechanisms. In addition, shelf life testing under accelerated and real-time conditions was conducted on sterile product in the final packaging configuration.

Test	Requirement	Results
Transducer Mechanical Reliability	Transducers subjected to 37°C environment with accelerated actuation signal for failures associated with mechanical fatigue. Test must demonstrate 8-year reliable life with 90% reliability and 90% confidence.	Passed
Transducer Environmental Reliability	Transducers subjected to elevated temperature/humidity/salinity environment with a typical drive signal providing a 16x Acceleration Factor for failures associated with exposure to the *implanted environment. Test must demonstrate* 8-year reliable life with 90% reliability and 90% confidence.	Passed
Sound Processor Battery Life	Sound Processors must demonstrate that following Shelf-life, the longevity must be at least 4.0 years, 5.5 years, and 2.0 year of operation before reaching BERI for continuous use, typical use, and worst-case use conditions, respectively.	Passed & Exceeded

Shelf Life Testing:
Accelerated and real time shelf life testing was conducted to validate a 2-year shelf life for all EtO sterilized components. For the Gamma sterilized EnvoyCem, accelerated shelf life testing was conducted to validate a 3-year shelf life.

Test	Requirement	Results
Accelerated shelf life – Packaging & Devices	Packaging to demonstrate barrier integrity following Maximum EtO Sterilization, Expanded Range Temperature Storage Conditions (the Age Accelerating Factor), and ASTM D4169 – Distribution Cycle 13. Barrier Integrity verified with Visual Inspection, Dye Penetration, & Seal Strength Devices to remain functional.	Passed
Real time shelf life – Packaging & Devices	Packaging to demonstrate barrier integrity following 2-year Real Time Testing in compliance with ISO 11607. Requiring packaging to satisfy requirements for: Visual Inspection, Dye Penetration, Seal Strength.	Passed

Temporal Bone Testing:
Temporal bone model was used to validate system performance.

Test	Requirement	Results
Implanted System Output Capability	The implanted system shall be capable of generating stapes displacement of at least 100 nm p-p over the range 500 Hz to 2000 Hz in a typical temporal bone model.	Passed
Output Limiting	The system shall be capable of limiting the maximum output displacement over at least a 20 dB range to accommodate patient physiology differences of efficacy and safety.	Passed
Programmable System Gain Range	The system shall have a typical unaided vs. aided stapes displacement gain programmable over at least the range 0 dB to 40 dB for frequencies between 500 Hz and 2000 Hz in a typical temporal bone model.	Passed

Software Verification/Validation
The Esteem Programmer, the Personal Programmer and the Intraoperative System Analyzer (ISA) contain software.

Off-the-shelf software is used for the operating system for the Esteem Programmer and ISA. Software development was conducted in conformance to FDA Guidance for Industry on Off-The-Shelf Software Use in Medical Devices (1999). Level of concern for the software used in the Esteem instrument components is minor, based upon the FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (2005).

Test	Requirement	Results
ISA Software	When used according to the labeling, the ISA software shall properly execute intraoperative measurements and display results.	Passed
Personal Programmer Firmware	When used according to the labeling, the Personal Programmer software shall properly communicate with the implanted device and provide visual indicators for the patient.	Passed
Esteem Programmer Software	When used according to the labeling, the Esteem Programmer software shall properly communicate with the implanted device, provide visual indicators for the clinician, and store programming information.	Passed

Conclusions of Preclinical Studies
The results of the Preclinical studies provided reasonable assurance that the Esteem system was safe for clinical studies and implantation in humans for its intended use.

B. Animal Studies

Early in the development of the Esteem, animal studies were conducted to research and evaluate the performance of the system. Prototype sensors were mounted in the middle ear of three chinchillas and followed for up to 98 days. Serial tympanometry and sensor voltage measurements were performed at three-week intervals. Results indicated that the chinchilla is a suitable model for long-term sensor implantation. The sensors appeared stable over time and frequency bandwidth. Histopathology showed no difference between the implanted ears and the controls. In order to verify the hermeticity and functionality of the Esteem under in vivo conditions, an animal implant study using a sheep was conducted. Four (4) Esteem devices, including Sound Processor, Sensor and Driver, were implanted in the back area of a sheep. Two (2) systems were explanted after 12 weeks and two (2) systems were explanted after 1 year. All systems were visually inspected and functionally tested after cleaning. There were no signs of corrosion or leakage noted; all functional testing indicated that the product performance was not affected by the in vivo implant conditions.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Esteem® device for alleviating hearing loss in subjects 18 years and older in the US under IDE # G070162. Data from this clinical study were the basis for the PMA approval decision. Additionally, the applicant performed an earlier clinical study (G000321) with the Esteem®. Although the PMA approval decision is based on G070162 alone, a description of both studies is given below.

Study Description (G070162)

In PMA submission P090018, the applicant presents data from a pivotal trial (IDE G070162) aimed at demonstrating the safety and effectiveness of the Esteem® system in subjects who have mild to severe hearing loss. This pivotal trial was designed as a prospective, multi-center, nonrandomized, clinical trial. Each of the 57 subjects implanted acted as both the test subject and the control by comparing his/her audiological test results and other measures prior to implant (under both unaided and aided conditions) to results at various time points after implantation.

Regulatory History

An earlier version of the Esteem® system was studied under a separate IDE (G000321). In the G000321 study, 72 total subjects were implanted at 6 investigational sites. Enrollment in this IDE has concluded. A number of G000321 subjects are now past their 3 and 4 year follow-ups. A high rate of failures (requiring 25 revision surgeries) was observed in this study, mainly due to inadequate bonding at the driver-stapes interface (17 events).

The current Esteem® system was studied under the IDE G070162. In order to address the high rate of failures observed in G000321, "Best Practices" (BP) for cleaning and drying was developed and used in the G000321 clinical post-BP subjects. In addition to the BP steps, a new 2-step EnvoyCem attachment procedure for the Driver and improved ISA testing are unique improvements to device implantation in the G070162 study. In this study, 57 subjects were implanted at 3 investigational sites. Of the 57 implanted subjects, 52 are past the 10 month follow up.

For a summary of key points of comparison between the G000321 study and the G070162 study, please refer to Table I below.

Table I. Key Points of Comparison between G070162 and G000321.

	G070162	G000321
Principle of Operation	No change	-
Device Design	Minor refinements of G000321 device, for example: • Single and dual channel frequency bands • Max gain 55 dB • Longevity 6 yrs nominal • Noise floor 23-28 dB SPL • Smaller personal programmer	• Single channel frequency band • Max gain 40 dB • Longevity 3.7 yrs nominal • Noise floor 30-35 dB SPL
Surgical Technique	Enhanced intraoperative techniques • 2 step cementing • Improved ISA testing	• Single step cementing • Original ISA procedure
Inclusion Criterion • Range of air conduction (AC) pure tone thresholds in the implanted ear • Speech discrimination test score	• Relatively wider (with respect to G000321) • > 40%	• Relatively more narrow (with respect to G070162) • > 60%
Implanted Subjects	57	72
1st Analysis of Endpoints	4 month post-activation	2 month post-activation
Primary Effectiveness Endpoints	SRT and WRS are the co-primary effectiveness endpoints.	SRT is the only primary effectiveness endpoint.
SRT Comparison (4 month post-activation)	Avg. 10.6 dB improvement (non-adjusted)	Avg. 3 dB improvement
Primary Safety Endpoints • Failures • Bone Conduction Analysis	• 3 failures in 3 unique subjects • Forehead placement	• 25 failures in 20 unique subjects • Mastoid placement

The applicant sought approval for this PMA based on the clinical data obtained under the G070162 study. As discussed above, differences in the surgical procedures precluded pooling of safety and effectiveness data from the two studies.

A. Study Design

Patient treatments were begun on January 22, 2008 and the patients continue to be followed. The database for this PMA reflected data collected through July 31, 2009 and included 60 patients. There were three investigational sites.

The study was a prospective, multi-center, one-arm, non-randomized, nonblinded study. The outcomes were compared to each subject's baseline pre-implanted hearing aided condition.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the G070162 study was limited to patients who met the following inclusion criteria:

   a) Subject is ≥ 18 years old.

   b) Subject understands the nature of the procedure and has signed the Subject Informed Consent Form prior to the procedure.

   c) Subject is willing and able to comply with specified follow-up evaluations and understands the audiological test procedures and use of the *Esteem® System.*

   d) Subject has mild to severe sensorineural hearing loss between 500 and 4000 Hz in the ear to be implanted with pure tone air conduction threshold levels within the limits of a Hearing Aid (HA) as follows:

Freq (Hz)	500	1000	2000	3000	4000
LL* (dB HL)	30	35	35	35	35
UL* (dB HL)	100	100	100	100	100

*LL = Lower Level; UL = Upper Level

   e) Subject's air-bone gap is no greater than 10 dB at 4 of the 5 following frequencies: 500, 1000, 2000, 3000 and 4000 Hz.

   f) Subject has an unaided maximum word recognition score of greater than or equal to 40% with recorded delivery using a phonetically balanced word list at SRT + 40 dB or at maximum tolerable presentation level.

   g) Subject is a current user of a properly functioning and appropriately fit hearing aid. This is defined as the subject has used this aid for at least four (4) hours (average) per day (in the ear to be implanted) for at least three (3) months for a new aid or one (1) month for an adjusted aid.

   h) Subject's hearing aid, in the ear to be implanted, shall appropriately fit optimally.

i) Subject has normally functioning Eustachian tube.

j) Subject has normal tympanic membrane.

k) Subject has a normal middle ear anatomy.

l) Subject has adequate space for *Esteem® System* implant determined via fine cut temporal bone CT scan.

m) Subject is a native speaker of the English language.

n) Subject is a hearing aid user in the ear to be implanted.

Patients were not permitted to enroll in the G070162 study if they met any of the following exclusion criteria:

a. Subject has a history of post-adolescent chronic middle ear infections, inner ear disorders or recurring vertigo requiring treatment, disorders such as mastoiditis, Hydrops or Meniere's syndrome or disease.

b. Subject has a history of otitis externa or eczema for the outer ear canal and the investigator believes this will affect the *Esteem® System* implantation.

c. Subject has cholesteatoma or destructive middle ear disease.

d. Subject has life expectancy of < two (2) years due to other medical conditions.

e. Subject has retrocochlear or central auditory disorders.

f. Subject is known to be suffering from any psychological, developmental, physical, or emotional disorder that the investigator feels would interfere with the surgery or follow-up testing.

g. Subject has a known history of fluctuating air conduction and/or bone conduction hearing loss over a one-year period of 15 dB in either direction at 2 or more frequencies (from 500 – 4000 Hz).

h. Subject has sudden hearing loss due to unknown cause.

i. Subject has a history of disabling tinnitus, defined as tinnitus which required treatment.

j. Subject is unable to adequately perform audiological testing.

k. Subject has a medical condition or is undergoing a treatment that may affect healing and the investigator does not believe the subject is a good candidate for the trial.

l. Subject has diabetes that is not well controlled with medication or diet and the investigator does not believe in his best medical judgment that the subject would be a good candidate for the trial.

m. Subject is pregnant at the time of device implant.

n. Subject has a history of keloid formation.

o. Subject has known hypersensitivity to silicone.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 4 and 10 months postoperatively.

Preoperative evaluations are listed in Table II. In this table, "Scr/BL" refers to the initial screening evaluation and baseline measurements.

"Proc/Disc" refers to the surgical procedure. "On" and "Act" refer to turning on the device and activating (programming) the device, respectively. "I" refers to the implant side, whereas "N" refers to the non-implant side.

The objective parameters measured postoperatively during the study are included in Table II. Clinical assessment occurred at 2 months, 4 months and 10 months post-operatively. In addition, clinical assessment occurred yearly. Adverse events and complications were recorded at all visits.

Table II. Screening and Follow-Up Requirements.

	Scr / BL	Proc / Disc	On	Act	2Mo	4Mo Endpt	10 Mo	Yearly
Informed Consent	X							
Medical History	X							
Audiological and Hearing Aid History	X							
Current Medications	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Device Settings			X	X	X	X	X	X

Testing Requirements								
Otogram Pre-screen Audiogical Test	X							
APHAB Questionnaire	X				X	X	X	X
Esteem Questionnaire					X	X	X	X
Otoscope Exam (perform prior to testing)	I		I	I	I	I	I	I
Tympanogram	I		I	I	I	I	I	I
Air Conduction Thresholds	I/N		I	I	I	I/N	I/N	I
Air Conduction – Aided (Implant) Ear Warble Tone	I							
Bone Conduction Thresholds	I/N		I	I	I	I/N	I/N	I
Most Comfortable Listening Level (MCL)	I/N			I	I	I	I	I
Uncomfortable Listening Level (UCL)	I/N			I	I	I	I	I
Speech Reception Threshold (SRT)– unaided	I/N							
Speech Reception Threshold (SRT)– aided	I/N			I	I	I	I	I

	Scr / BL	Proc/ Disc	On	Act	2Mo	4Mo Endpt	10 Mo	Yearly
Word Recognition – unaided	I/N							
Word Recognition – aided	I/N			I	I	I	I	I
Quick SIN – Aided	I/N			I	I	I	I	I
Quick SIN – Unaided	I/N							
Envoygram IT			X	X	X	X	X	X
CT Scan	X							
X-ray of implanted device		X						

I=Implanted Ear N=Non-Implant Ear

3. Clinical Endpoints

Co-Primary Safety Objective – Serious Adverse Device Effects
To determine the incidence of Serious Adverse Device Effects (SADE) and the incidence rate of device failures and replacements.

Endpoints: The analysis of the incidence of SADEs and device failures and replacements through the 4–month and 10-month post-activation follow-up.

Hypotheses: This objective was to provide an accurate estimate of the SADE rate and device failure and replacement rate associated with the Esteem® System. Therefore, no formal hypothesis tests were conducted.

Adjudication of Adverse Events, SADEs, and Device Failures:

Adverse Events were collected throughout the Pivotal Trial. Envoy Medical established a Clinical Events Committee (CEC) that adjudicated clinical adverse events for the Esteem clinical trial.

The CEC was responsible for establishing and approving decision rules and definitions for the determination of clinical adverse events using data collected *on* Case Report Forms (CRF's) in the trial. The CEC reviewed all AEs and classified each event as serious or not serious and as device related, procedure related, pre-existing, or not related.

The members of the CEC are physicians/PhDs drawn from the Ear, Nose & Throat (ENT) medical community. The CEC is made up of three voting members. At the time of review, there were two otolaryngology surgeons and one audiologist on the CEC. A representative from Envoy Medical chaired the committee meetings, but Envoy Medical states that the CEC chair did not vote during adjudication of AEs.

Definitions

The protocol used the following definitions of various categories of Adverse Events.

Adverse Event (AE)

An Adverse Event is any undesirable clinical event occurring to a subject, during a clinical trial, whether or not it is considered related to the investigational product. This includes a change in a subject's condition or laboratory results, which has or could have a deleterious effect on the subject's health or well being.

Adverse Device Effect (ADE):

An Adverse Device Effect is an Adverse Event related to the investigational device.

Unanticipated Adverse Device Effects (UADE)

An Unanticipated Adverse Device Effect is any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious Adverse Event (SAE) or Severe Adverse Device Effect (SADE)

A Serious Adverse Event (SAE) or Serious Adverse Device Effect (SADE), are events which:

- Result in death
- Is life threatening
- Requires inpatient hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment/damage

Co-Primary Safety Objective – Cochlear Stability
To demonstrate that the subjects' cochlear function remains unchanged with the Esteem® System as shown by comparison of the subjects' pre-implant baseline bone conduction threshold (BCT) versus the subjects' 4-month and 10-month post-activation BCT.

Endpoint Analysis: Average and individual changes were evaluated per the protocol. Bone conduction was measured with forehead probe placement. Stability was defined as bone conduction threshold change to be within ± 10 dB.

Note: A Safety Algorithm was adopted to measure cochlear stability for any bone conduction results outside the stability range. This Safety Algorithm can be located in Appendix 1 (Section X) below.

Co-Primary Primary Effectiveness Objective – Speech Reception Threshold
To demonstrate that the Esteem® System improves the speech reception threshold of sensitivity for hearing and identifying speech signals as well as or better than the pre-implant hearing aid (aided condition).

Endpoint: Comparison of the speech reception threshold (SRT) using the Esteem® System (4 months post activation) as compared to the pre-implant aided condition.

Hypothesis: The 95% Lower Confidence Bound (LBC) for the mean of difference between the SRT at baseline versus four months is greater than or equal to -5 dB.

$$95\%\ \text{LCB for Mean}(\text{Pre-implant aided} - \mu\ 4\ \text{month}) \geq -5$$

Co-Primary Effectiveness Objective – Word Recognition Scores
To demonstrate that the Esteem® System at the 4 months postactivation visit is as effective as or better than the hearing aid for improving speech discrimination (intelligibility) as shown by the word recognition score at 50 dB HL.

Endpoint: Comparison of the word recognition score (WRS) using the Esteem® System at 4 months post-activation compared to the pre-implant aided condition.

Hypothesis: This objective was to provide a comparison of the WRS at 50 dB HL associated with the Esteem® System versus the baseline aided condition. There is no formal hypothesis and descriptive statistics are to be presented.

Statistical Analysis: The Word Recognition Scores will be compared using the Thornton and Raffin (1978) published upper and lower limits for various word lists based upon percentage scores. An analysis showing the "% better than", "% equal to", and "% below" the aided condition (HA) will be presented.

Reference: Thornton AR, Raffin MJ. Speech discrimination scores modeled as a binomial variable. J Speech Hear Res 1978; 21:507-18.

Secondary Effectiveness Objectives

No hypothesis testing was pre-specified for any of the secondary endpoints in the protocol.

Pure Tone Average (PTA)

To demonstrate that the Esteem® System at the 4 month post activation visit improves the 3-frequency (500, 1000, and 2000 Hz) pure tone average (PTA) when compared to the baseline unaided condition.

QuickSIN

To demonstrate that the Esteem® System at the 4 month postactivation visit is as effective as or better than the hearing aid for improving speech discrimination (intelligibility) as shown by the QuickSIN (speech in noise) test results.

APHAB Quality of Life (QOL)

To show that the Esteem® System improves Quality-of-Life when compared to the baseline aided condition as shown by APHAB scores.

Esteem Questionnaire Quality of Life (QOL)

To gather subject feedback and comments on the use of the Esteem® System relative to the pre-implant hearing aid (aided condition) as shown by the Esteem® Questionnaire.

B. Accountability of PMA Cohort

For the pivotal study (G070162), 57 of 60 enrolled subjects were successfully implanted with the study device at three study sites: 22 subjects at Southeastern ENT & Sinus Center in Greensboro, NC; 18 subjects at Shohet Ear Associates Medical Group in Newport Beach, CA; and 17 subjects at Lahey Clinic in Burlington, MA (Table III). Among the 57 implanted subjects, 54 subjects completed the 4-month follow-up (3 subjects had revision surgery due to limited benefit and were excluded from the analysis of the primary and secondary effectiveness outcomes) and 52 subjects completed the 10-month follow-up.

Of the 60 enrolled subjects, three were not implanted. Two patients were enrolled, underwent surgery, but did not receive the implant because the middle ear space was inadequate. A third subject decided to withdraw from the study after signing the consent form.

Of the 57 implanted subjects, three did not make the 4-month follow-up because of revision surgery.

Of the 54 subjects who reached the 4-month follow-up, two subjects did not reach the 10-month follow-up. The first of these subjects was explanted due to an incision breakdown that would not heal (possibly related to a smoking habit). A second subject had not been scheduled for the 10-month follow-up at the time the data base was finalized.

Table III. Patient Accountability by Site and Follow-Up Visit.

	Total Implanted	4-month Follow-Up N (%)	10-month Follow-Up N (%)
All	57	54 (94.7)	52 (91.2)
Southeastern ENT & Sinus Center	22	21 (95.5)	21 (95.5)
Shohet Ear Associates Medical Group	18	18 (100.0)	16 (88.9)
Lahey Clinic	17	15 (88.2)	15 (88.2)

C. Study Population Demographics and Baseline Parameters

The subject demographic data is summarized in Table IV. The subjects' average age was 52.9 years, ranging from 18 to 77 years; 67% (38) were male and 33% (19) were female. Fifty six (56) of the 57 implanted subjects with available baseline data were Caucasian (98%), and one subject was Asian. At the time of study enrollment 25% (14) were retired, 9% (5) worked part time, and 51% (29) worked full time. Fifty four

(54) of the 57 subjects (95%) suffered a gradual hearing loss that was diagnosed at an average age of 32.5 years, ranging from 1 to 66 years.

The degree of hearing loss, based on pure tone average (PTA), was mild in 3 subjects, moderate in 44 subjects and severe in 10 subjects (Table IV). All 57 (100%) subjects were current users of a hearing aid with average usage time of 13.7 years, ranging from 0.4 to 37.8 years. Of the subjects implanted, 49 (86%) subjects used hearing aids in both ears.

Table IV. Subject Demographics and Degree of Hearing Loss.

Demographics	Mean ± SD n (min, max)	Degree of Hearing Loss (implanted ear)	N/Total (%)
Age (years)	52.9 ± 15.8 57 (18.0, 77.2)	Mild (PTA ≤ 40 dB) Moderate (41 dB < PTA ≤ 55 dB)	3/57 (5.3%) 25/57 (43.8%)
	N/Total (%)	Moderate Severe (56 dB < PTA ≤ 70 dB)	15/57 (26.3%)
Gender		Severe (PTA > 71 dB)	10/57 (17.6%)
Male	38/57 (66.7%)		
Female	19/57 (33.3%)		
Race/Ethnicity			
White/Caucasian	56/57 (98.2%)		
Black/Non-Hispanic	0/57 (0%)		
Hispanic	0/57 (0%)		
Asian	1/57 (1.8%)		
Work Status			
Full Time Employee	29/57 (50.9%)		
Part Time Employee	5/57 (8.8%)		
Retired	14/57 (24.6%)		
Unemployed	4/57 (7.0%)		
Other	5/57 (8.8%)		

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 60 subjects.. The key safety outcomes for this study are presented below in Tables V to XIV and Figure 2. Adverse effects are reported in Tables V, VI, IX, XI-XIII, and Figure 2.

Adverse effects that occurred in the PMA clinical study:

Severe Adverse Device Effect (SADE)

The CEC determined that there were 6 SADEs reported in 6 subjects, for an incidence of 10.5% (6/57), as shown in Table V. Among the SADEs, three were due to limited benefit which resulted in revision procedures. One subject had incision site infection. One other subject had incision breakdown. The sixth subject experienced severe pain and facial weakness which resolved with medication.

Table V. Severe Adverse Device Effects (SADEs). Co-Primary Safety Endpoint.

Subject #	Event	Total Number	Intervention	Status
103-24 MIEKU	Severe pain and Facial Weakness	1	Medication	Resolved
109-34 CHWYA	Incision Site Infection	1	Medication	Resolved
103-22 JELGR 102-22 DAAKU 109-24 CRBAR	Limited Benefit	3	Revision Procedures with replacement of parts of the Device	1 Subject has reached 4 month Endpoint, Remaining 2 Subjects have reached 2 month post-operative period, but not the 4 month Endpoint at the time of this report
105- 37 LADGO	Incision Breakdown	1	Required Explantation	Reconstructed with Incudoplasty
Total SADE Events		6		

For more detail concerning the 3 patients with Limited Benefit and 1 patient who required explantation, refer to Table VI.

Table VI. Device Failure/Revisions/Explants and Reconstruction.

Subject.#	Event	Implant Date	Elapsed time to resolution	Revision/ Explant Date	Findings at Surgery	Reimplant /Reconstruction Method
103-22 JELGR	Limited Benefit shortly after Activation	1/30/08	8.5 months	10/16/08	Fibrous Adhesions fixing sensor to incus and Driver Additional observation: MedCem butted against the short process of incus causing lower than expected Sensor and ISA test performance at implant.	Replaced Sound Processor and Sensor
109-22 DAAKU	Limited Benefit at Activation	5/16/08	12.5 months	5/29/09	Extensive Fibrous adhesions in the facial recess surrounding the Driver and stapes. Additional observation: An unusually small amount of EnvoyCem was present to form the Driver to Stapes connection.	Replaced Sound Processor and Driver
109-24 CRBAR	Limited Benefit.	5/30/08	11 months	5/01/09	Extensive Fibrous adhesions noted in the facial recess surrounding the Driver and stapes. Additional findings: Driver tip pulled away from stapes & unusually small amount EnvoyCem	Replaced Sound processor and Driver
105-37 LAGDO	Repeated Incision breakdown	6/27/08	8months	2/27/09	Incision had a large opening under the scab	Reconstructed with Incudoplasty

Device Failure Summary
A failure summary was presented by the applicant for 3 subjects that received Limited Benefit from the device as follows:

Subject 103-22 JELGR reported a decrease in benefit shortly after Activation, continuing through the 2-month follow-up visit. Diagnostic testing indicated that the Sensor output was lower than normal. The revision procedure found extensive dense fibrous adhesions filling the facial recess. The fibrous adhesions had fixed the Sensor to the incus and the Driver to the malleus. In order to remove the fibrous adhesions, the surgeon had to remove the Sensor and Driver and replace them with new components. During this process, surgeon noticed some MedCem butted against the short process of the incus, restricting its movement. He removed this obstruction in order to restore mobility of the incus. The new Sensor, Driver and System tests were conducted with acceptable results. The surgeon's conclusion was that the dense fibrous adhesions that formed after implant prevented the Sensor and incus from moving properly causing the poor performance. The MedCem attached to the incus likely was the cause of lower than expected Sensor and System ISA test performance at implant but as indicated by the data the fibrous adhesions that developed after Activation were the cause of the decrease in benefit.

Subject 109-24 CRBAR reported limited benefit at Activation that progressively worsened through the 2-month follow-up. Diagnostic testing indicated that the Driver output was lower than normal. The revision procedure showed extensive fibrous adhesions in the facial recess surrounding the Driver and stapes. The Sensor was functioning properly and not affected by the adhesions. During removal of the fibrotic tissue, The surgeon found that the Driver tip had been laterally pulled away from the stapes EnvoyCem connection and that an unusually small amount of EnvoyCem was present to form the Driver-stapes connection. This subject had a small facial recess opening that could have affected visibility and the original application of EnvoyCem. The surgeon implanted a new Driver and used EnvoyCem to complete the connection to the stapes. The new Driver, Sensor and System tests were conducted with acceptable results. The conclusion was that the fibrous adhesions that formed after implant likely prevented the Driver and stapes from functioning properly causing the limited benefit.

Subject 109-22 DAKKU reported limited benefit at Activation that progressively worsened through the 2-month follow-up. Diagnostic testing indicated that the Driver output was lower than normal. The revision procedure showed extensive fibrous adhesions in the facial recess surrounding the Driver and stapes. The Sensor was functioning properly and not affected by the adhesions. During removal of the fibrotic tissue, the surgeon found that an unusually small amount of EnvoyCem was present to form the Driver-stapes connection. This subject had a small facial recess opening that could have affected visibility and the original application of EnvoyCem. The surgeon implanted a new Driver and used EnvoyCem to complete the connection to the stapes. The new Driver, Sensor and System tests were conducted with acceptable results. The conclusion was that the fibrous adhesions that formed after implant likely prevented the Driver and stapes from functioning properly causing the limited benefit.

Bone Conduction Threshold - Cochlear Stability

The objective was to demonstrate that the subject's cochlear function remains unchanged with the Esteem® System as shown by comparison of the subject's pre-implant baseline Bone Conduction Threshold (BCT) vs. the subject's 4-month and 10-month post-activation BCT. Average and individual changes were evaluated per the protocol. Bone conduction was measured with forehead probe placement. Stable results should be within ± 10 dB. A Safety Algorithm (Appendix 2) was adopted to measure cochlear stability for any bone conduction results outside the stability range.

At the group level, changes in bone conduction threshold were used to determine whether the Esteem® System caused damage to residual cochlear function. The average 3-frequency (500, 1000, 2000 Hz) bone conduction change from baseline for all subjects was 0.1 ± 0.9 dB (mean ± standard error) at 4 months and -0.8 ± 1.1 dB (mean ± standard error) at 10 months (Table VII). This small change is indicative of no systemic cochlear damage being caused by either the implant or the therapy.

Table VII. Average Bone Conduction Threshold Results (reported as mean +/- standard error).

	500 Hz mean ± se (CI range)	1000 Hz mean ± se (CI range)	2000 Hz mean ± se (CI range)	4000 Hz mean ± se (CI range)	PTA mean ± se (CI range)
Pre-Implant	45.0±1.9 (41.3, 48.7)	57.5±1.7 (54.1, 60.8)	66.6±1.4 (63.7, 69.4)	65.0±1.7 (61.5, 68.5)	56.3±1.3 (53.7, 58.9)
4-Month	45.4±1.9 (41.7, 49.1)	57.9±1.6 (54.6, 61.1)	67.4±1.3 (64.8, 70.0)	65.6±1.5 (62.6, 68.6)	56.4±1.3 (53.7, 59.0)
Mean Difference	0.0 ± 0.9 (-1.8, 1.8)	0.0 ± 1.0 (-2.0, 2.0)	2.2 ± 1.3 (-0.4, 4.8)	1.2 ± 1.2 (-1.3, 3.7)	0.1 ± 0.9 (-1.7, 2.0)
10-Month	42.6±2.0 (38.7, 46.5)	56.9±1.6 (53.8, 60.1)	68.0±1.4 (65.2, 70.7)	66.3±1.5 (63.4, 69.3)	55.3±1.5 (52.3, 58.3)
Mean Difference	-2.3±1.0 (-4.4, -0.3)	-0.3±1.2 (-2.7, 2.0)	1.3±1.4 (-1.5, 4.1)	2.2±1.3 (-0.5, 4.8)	-0.8±1.1 (-3.1, 1.5)

There was no mean change in bone conduction threshold at 4-months relative to the baseline for frequencies 500 and 1000 Hz (0.0 ± 6.4 dB, 0.0 ± 7.0 dB, respectively; mean ± standard deviation). There were slight increases in the bone conduction threshold for frequencies 2000 and 4000 Hz (2.2 ± 7.8 dB, and 1.2 ± 7.6 dB, respectively; mean ± standard deviation).

At the individual level, all subjects with 4-month and 10-month data in the database as of July 27, 2009, were analyzed according to the change criteria adopted in bone conduction (BC) and safety algorithm (SA) in accordance with the clinical protocol (i.e., 2 out of 4 frequencies change greater than 10 dB or 1 frequency greater than 20 dB; for details, see Appendix 2). Out of 54 subjects who had 4-month follow-up, the BC/SA threshold could not be determined in two subjects (0204-103-34-CYJTA and 0204-109-27-BRTGR) at one or more frequencies due to equipment limits. For the remaining 52 subjects, no subjects had a BC/SA threshold shift at the 4-month endpoint greater than the protocol criteria. At 10 months, the applicant reported that 52 subjects had the BC/SA data. The BC/SA threshold could not be determined at one or more frequencies in one subject (0204-109-27-BRTGR) due to equipment limits. Of the 51 subjects, one subject (0204-103-28-TOSTR) had a BC/SA threshold shift of greater than 20 dB at 4000 Hz.

The more consistent and stable bone conduction measurements in G070162 compared to G000321 may be due to the forehead probe placement versus the mastoid probe placement. Bone conduction was shown to be stable through the 4- and 10-month intervals.

In a worst-case scenario under the intent to treat population, 13% (8 out of 60) and 15% (9 out of 60) of the study cohort does not meet this safety objective at 4- and 10-month follow-up, respectively. At the 10-month follow-up, one subject (103-28) had a BC/SA threshold shift greater than the protocol criteria at the 4000 Hz.

A summary of clinical safety outcomes is provided in Table VIII.

Table VIII. Summary of Clinical Safety Data.

Clinical Protocol Objectives	4 Month Results	10 Month Results
Primary Safety Objective: • Serious Adverse Device Effects (SADE) • Incidence of Device Failures and Replacements	SADE • Three (3) subjects for facial weakness / incision issues • Three (3) subjects for revision procedures to date • SADE rate: 10.5% (6 of 57) Failures • Three (3) failures resulting in approved revisions were reported in three unique subjects prior to the 4-month follow-up • Failure rate: 5.3% (3 of 57)	SADE • No additional SADE were reported between the 4-month and 10-month follow-up visits Failures • No additional failures were reported between the 4-month and 10-month follow-up visits
Primary Safety Objective: • Bone conduction (BC) threshold at 4 months post-activation vs. pre-implant • Safety Algorithm (SA) for those that fail BC	Bone Conduction • Average 3 frequency (500, 1K, 2K) bone conduction change of 0.1 dB at 4 months vs. pre-implant. • Individually, no subjects (0) at 4 months had BC/SA change per the protocol criteria from pre-implant.	Bone Conduction • Average 3 frequency (500, 1K, 2K) bone conduction change of -0.8 dB at 10 months vs. pre-implant. • Individually, one subject (1) at 10 months had BC/SA change per the protocol criteria from pre-implant at 4 kHz.

Adverse Event Results

The list of reported adverse events related to the device as determined by the CEC are shown in Table IX (as provided by the applicant in the PMA):

- 96 ADEs were reported in Table IX if they were found during CEC adjudication to be not serious and were found to be caused by the mastoidectomy w/facial recess, device, peri-operative surgery related, or device implant procedure related.
- The majority of these Adverse Effects were classified as mild or moderate.
- 70% of the ADEs have resolved.
- The remaining 30% of the ADEs are ongoing for over a year at the time of this report. Ongoing ADEs include conditions like taste disturbance, facial weakness/paralysis, tinnitus, dizziness, middle ear effusion, and ear pain.

The list of reported adverse events that are not device related as determined by the CEC are shown in Table X:

- Events were classified as AE's if they were found during CEC adjudication to be caused by underlying or concomitant illness, concomitant medications, or other causes.
- Seventeen events were classified as mild, 4 as moderate, and 1 as severe.
- Of the 29 AEs reported, 21 (72%) have resolved.
- 8/29 AEs (28%) were still ongoing at the time of this report.

Table IX. CEC-adjudicated Adverse Device Effects (96 Events in 43 Subjects).

Event	Mild	Moderate	Severe	Total
Aural Fullness	2	0	0	2
Blistering TM	1	0	0	1
Chest Pain	1	0	0	1
Discomfort above Incision	1	1	0	2
Dizziness	1	0	0	1
Dry Eye	1	0	0	1
Disequilibrium	3	0	0	3
Ear Cracking	2	0	0	2
Ear Pain	4	0	0	4
Ear Roaring	1	0	0	1
Eye Irritation	1	0	0	1
Eye Squint	1	0	0	1
Facial Weakness/Paralysis	2	1	0	3
Feedback	1	0	0	1
Fluid	3	6	0	9
Headache	1	1	0	2
Imbalance	1	0	0	1
Incision Discomfort	3	0	0	3
Incision Drainage	1	0	0	1
Limited Benefit	1	0	0	1
Metallic Taste	1	0	0	1
Middle Ear Effusion	8	0	0	8
Moist Debris	1	0	0	1
Nasal Drainage	1	0	0	1
Noise	1	0	0	1
Numbness	1	0	0	1
Otitis Externa	2	0	0	2
Otalgia	2	0	0	2
Pain	2	0	0	2
Taste Disturbance	23	1	0	24
Tinnitus	8	0	0	8
TM Perforation	1	0	0	1
Tongue Numbness	1	0	0	1
Unsteadiness	1	0	0	1
Vertigo	0	1	0	1
TOTAL	85	11	0	96

Table X. CEC-Adjudicated Adverse Events (29 Events in 25 subjects).

Event	Mild	Moderate	Severe	Total
Apnea	1	0	0	1
Dizziness	1	0	0	1
Ear Canal Wound (non-implant ear)	0	0	1	1
Eustachian Tube Dysfunction	1	0	0	1
Headache	1	0	0	1
Imbalance	1	0	0	1
Knee Pain	1	0	0	1
Light Headedness	1	0	0	1
ME Effusion	1	0	0	1
ME Fluid	1	0	0	1
Motor Vehicle Accident	1	0	0	1
Mucosal Inflammation	0	1	0	1
Nose bleed	2	0	0	2
Pain	0	1	0	1
Post Nasal Drainage	1	0	0	1
Rapid Heart Rate	1	0	0	1
Rash Abdominal	1	0	0	1
Root Canal	1	0	0	1
Sinus Infection	2	0	0	2
Sprained Ankle	0	1	0	1
Touch Sensation	1	0	0	1
Tinnitus	0	1	0	1
URI	2	0	0	2
Vertigo	2	0	0	2
Yeast infection	1	0	0	1
TOTAL	24	4	1	29

Table XI, Table XII, Table XIII, and Figure 2 have been compiled by FDA from a spreadsheet provided by the applicant which includes all adverse events. All events have been grouped into 9 broad categories of Taste, Middle Ear Effusion, Pain, Tinnitus, Imbalance/Dizziness, Facial Paresis, Limited Benefit, Headache, and Miscellaneous. Table XII summarizes all 133 adverse events observed during this study and subject status at the time of this PMA submission. Table XII presents a detailed description of the adverse events in each of the 9 categories. The following observations can be made from these two tables:

- Of the 133 adverse events, 78% have resolved, 21% remain unresolved, and the status of 1 event is unknown.
- The most frequent adverse event was taste disturbance (24 of 57 subjects, 42%). This adverse event has not resolved for 8 subjects (14%).
- Facial paresis/paralysis was reported in 7% of subjects with 1% still reported to be ongoing after one year.

- 52 (91%) of 57 subjects experienced AEs; 36 of 52 Subjects experienced multiple (2-8) AEs, not all events are resolved; 26 Subjects have ongoing AEs.

Table XI. Categories of Adverse Events and Status.

Adverse Event (AE) Categories	Number of AEs (% of total AEs)	Number of Subjects *with AEs* (% of 57 implanted subjects)	Number of Resolved AEs (% of category)	Number of Subjects with Resolved AEs (% of 57 implanted subjects)	Number of AEs Ongoing (% of category)	Number of Subjects with *Ongoing* AEs (% of 57 implanted subjects)	Number of AEs with Resolution Status Unknown (% of category)	Number of Subjects with Resolution Status Unknown (% of 57 implanted subjects)
Taste Distur-bance	25 (19%)	24 (42)%	16 (64%)	15 (26%)	8 (32%)	8 (14%)	1 (4%)	1 (2%)
Middle Ear Effusion	18 (14%)	18 (32%)	18 (100%)	18 (32%)	0	0	0	0
Pain	12 (9%)	12 (21%)	8 (67%)	8 (14%)	4 (33%)	4 (7%)	0	0
Imbalance/ Vertigo /Dizziness	11 (8%)	11 (19%)	9 (82%)	9 (16%)	2 (18%)	2 (4%)	0	0
Tinnitus	10 (8%)	10 (18%)	7 (70%)	7 (12%)	3 (30%)	3 (5%)	0	0
Facial Paresis/ Paralysis	4 (3%)	4 (7%)	2 (50%)	2 (4%)	2 (50%)	2 (4%)	0	0
[illegible]nited [illegible]nefit	4 (3%)	4 (7%)	4 (100%)*	4 (7%)	0	0	0	0
Headaches	3 (2%)	3 (5%)	3 (100%)	3 (5%)	0	0	0	0
Miscella-neous	46 (34%)	30 (52%)	37 (80%)	**	9 (20%)	**	0	0
Total	**133 (100%)**	**52 (91)%**	**104(78%)**	***	**28 (21%)**	***	**1 (.008%)**	**1 (2%)**

***1 Subject resolved without intervention, 1 Subject has reached the 4 month Endpoint; 2 Subjects have only reached 2 month post-operative period, but not the 4 month Endpoint at the time of this report.**
**** 12 of 30 Subjects (40%) experienced 2-4 AEs in Miscellaneous category, not all events resolved; 12 Subjects have ongoing AEs**
***** 36 of 52 Subjects experienced 2-8 AEs, not all events resolved; 26 Subjects have ongoing AEs**

Table XII. Description of Adverse Events with Categories.

Adverse Event Category	Description of Adverse Event	Number of Events
Taste Disturbance		**25**
	Taste Disturbance	18
	Metallic Taste	3
	Altered Taste	1
	Disturbed Taste	1
	Taste Disturbance	1
	Taste Disturbance (*Delayed Onset*)	1
Middle Ear Effusion		**18**
	Middle Ear Fluid	5
	Effusion	3
	Fluid Behind TM	2
	Crackling Sound	1
	Crackling Drainage Sound	1
	Effusion (R)	1
	Fluid AS	1
	Middle Ear Effusion	1
	Middle Ear Fluid	1
	Middle Ear Effusion , Rt. Ear, Implant Ear	1
	Residual Effusion L Middle Ear	1
Pain		**12**
	Otalgia	2
	Discomfort Above Implant	1
	Discomfort/Pain R Side of Head	1
	Ear Canal Pain	1
	Ear Pain	1
	Ear Pain/Pressure	1
	Intermittent Otalgia	1
	L Ear Pain	1
	Pain Around Incision	1
	Pain in Temporal Region /Cheek	1
	Pain/Incision discomfort	1
Vertigo/Dizziness/Imbalance		**11**
	Vertigo	3
	Dysequilibrium	2
	Imbalance	1
	Mild Dysequilibrium	1
	Unsteadiness	1
	Unsteadiness	1
	Dizziness	2
Tinnitus		**10**
	Tinnitus Left Ear	2
	Right Ear Roaring	1
	Slight Increase in Tinnitus	1
	Tinnitus Left Ear	1
	Tinnitus	5
Facial Paresis		**4**

	Facial Palsy	1
	L Facial Paresis	1
	Facial Weakness	1
	R Facial Weakness	1
Limited Benefit		**4**
	Limited Benefit *	1
	Limited Benefit **	1
	Limited Benefit **	1
	Limited Benefit **	1
Headaches		**3**
	Headache	1
	Headache	1
	Frontal Headache	1
Miscellaneous		**46**
	Aural Fullness	2
	Nose Bleed	2
	Sinus Infection	2
	Motor Boat Sound/Shorting Out of Sound	2 (1 each)
	URI	2
	Ankle Trouble/Broken leg	2 (1 each)
	Apnea (pre-existing)	1
	Incision Breakdown (1), Infection(2), and Discomfort (1)	4
	Nasal Drainage/Post Nasal Drip	2 (1 each)
	TM Perforation/TM Blistering	2 (1 each)
	Otitis Externa (1), Debris in Ear Canal (2), and Sore in Ear Canal (1)	4
	Eustachian Tube Dysfunction/Feedback	2 (1 each)
	TIA, Chest Pain, Knee Pain, Pregnancy, MVA	5 (1 each)
	Rapid Heart Beat, Rash, Tooth Pain	3 (1 each)
	Yeast Infection, Discomfort, Light Headedness	3 (1 each)
	Hair Follicle Incision and Blood Fluid (L)	2 (1 each)
	Dry Eye, Eye Irritation, Eye Squint	3 (1each)
	Numbness, Numbness of left Tongue, Numbness of Tongue	3 (1 each)
Grand Total		**133**

*** One Subject with Limited Benefit improved without intervention**
**** Three Subjects with Limited Benefit underwent revision surgery**

Figure 2 represents the breakdown of adverse events by each of the three sites. Table XIII verifies that Site 109 has very few ongoing Adverse Events as compared to Site 103 and 105. Figure 2 and Table XIII show that there is wide variability of reported Adverse Events across the three sites that participated in this study.

Table XIII. Status of Adverse Events by Clinical Site.

Adverse Events	Site 103	Site 105	Site 109	Grand Total
Not Resolved, No Follow Up Necessary		1		1
Ongoing at the Time of Report	15	19	3	37
Recovered, No Residual Effects	35	45	14	94
Unknown		1		1
Grand Total	50	66	17	133
Number of Subjects Implanted	N=22	N=18	N=17	N=57

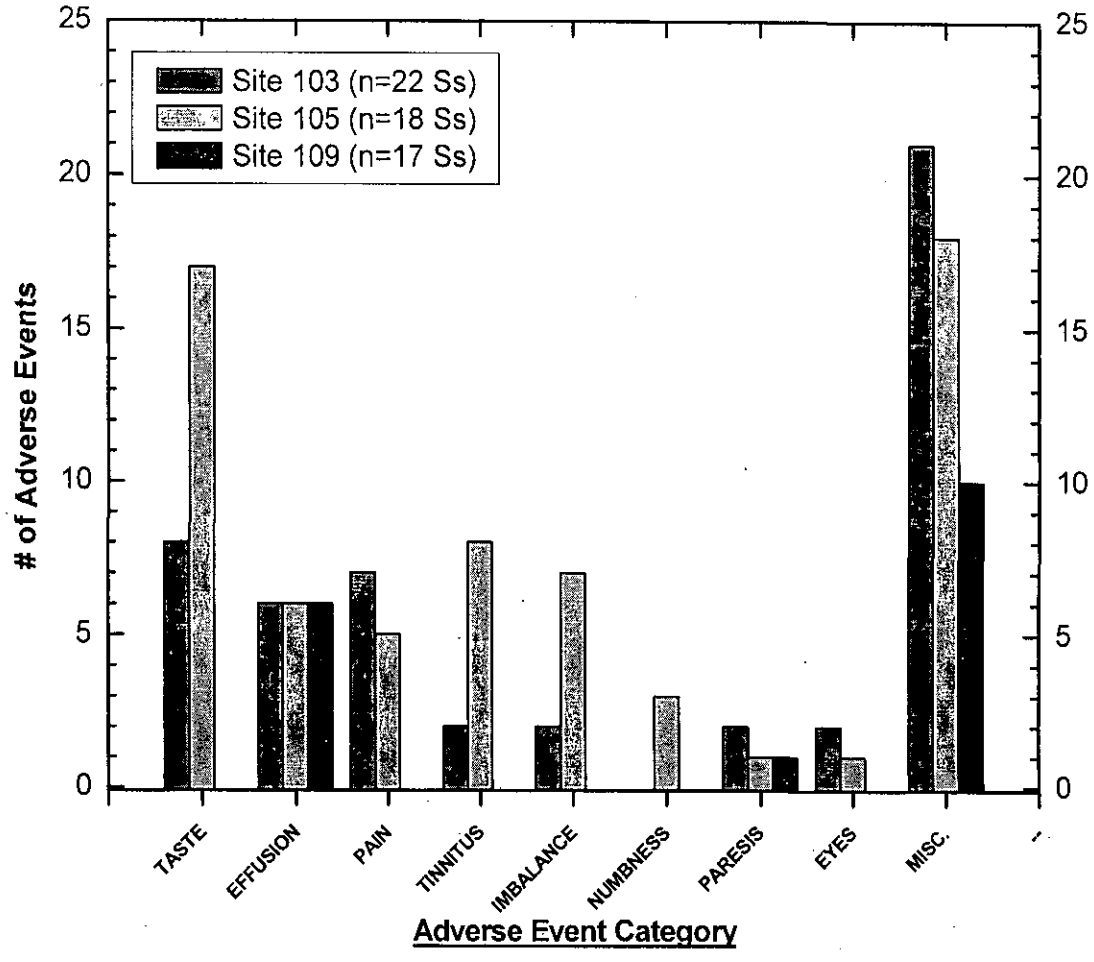


Figure 2. Numbers of adverse events grouped by category and site.

Unanticipated Adverse Device Effect (UADE)

The Clinical Events Committee (CEC) determined that there were no UADEs reported during this trial.

Severe Adverse Events (SAE)
A total of two events have been reported which were classified as SAEs:

- Broken leg (recovered)
- Transient ischemic attack (recovered)

2. Effectiveness Results

Speech Reception Threshold (SRT)
The criterion used is that the 95% Lower Confidence Bound (LBC) for the mean of difference between the SRT at baseline versus four months is greater than or equal to -5 dB.

The mean SRT decrease at 4 months from baseline (pre-implant, aided) was 10.6 with a 95% confidence interval ranging from 7.1 to 14.2 (Table XIV).

Table XIV. Mean Improvement in SRT Scores at 4 and 10 Months (Unadjusted).

Follow-up Period	SRT (in dB) mean ± se n (min, max)		
	Pre-Implant Aided	4-Month	10-Month
	41.2 ± 1.5 57 (38.3, 44.1)	30.6 ± 1.6 54 (27.4, 33.7)	29.4 ± 1.6 52 (26.1, 32.7)
Mean Improvement (95% CI)	NA	10.6 ± 1.8 (7.1, 14.2)	11.4 ± 1.8 (7.7, 15.2)

However, as shown in Table XV the heterogeneity in the treatment effect among sites is statistically significant (p-value < 0.01). Overall, the mean SRT improvement with the Esteem® compared to the preimplant hearing aid was 10.6 dB with the site-specific mean improvement between 1.3-16.9 dB.

Table XV. Mean Speech Reception Threshold (SRT) Decrease at 4-Months Relative to the Baseline (Aided Condition) for the Three Investigational Sites.

Analysis	Site 103 Mean±SE	Site 105 Mean±SE	Site 109 Mean±SE	P-value for Site Differences
Unadjusted	11.9±2.6	16.9±2.8	1.3±3.0	<0.01

Word Recognition Score

The applicant's objective was to demonstrate that the Esteem® at the 4 months post-activation visit is as effective as or better than the hearing aid for improving speech discrimination (intelligibility) as shown by the word recognition score at 50 dB HL.

The endpoint was the comparison of the word recognition score (WRS) using the Esteem® at 4 months post-activation compared to the pre-implant baseline aided condition. The applicant indicated that the objective of WRS was to provide a comparison of the Word Recognition Scores at 50 dB HL associated with the Esteem versus the baseline aided condition. The applicant did not propose any formal hypothesis, and the WRS was analyzed using the method described by Thornton and Raffin (Speech discrimination scores modeled as a binomial variable; J Speech Hear Res 1978; 21:507-18) regarding upper and lower limits for various word lists based upon percentage scores. An analysis showing the "% better than", "% equal to", and "% below" the pre-implant baseline aided condition was presented.

As reported, Table XVI displays the WRS results at the 4- and 10-month intervals. At 4 months, 93% of the subjects' WRS was as good as or better than that in the aided baseline condition (HA), and 7% exhibited below. The percentage of subjects having equivalent or better than HA decreased to 88% at 10 months, and those exhibiting below HA increased to 12%.

Table XVI. Word Recognition Scores (WRS) at 50 dB HL.

	All Subjects	
	4 Month N=54	10 Month N=52
% Better HA	30/54 (56%)	32/52 (62%)
% = HA	20/54 (37%)	14/52 (27%)
% Below HA	4/54 (7%)	6/52 (12%)

The mean change in WRS at the 4-month visit was 21.7%, with a 95% confidence interval of 13.3 to 30.1 (Table XVII). However, as also observed in the SRT endpoint data, there is statistically significant heterogeneity in WRS among the sites (Table XVIII, p=0.01). The mean change in WRS at 4-months varied from 3.6 to 37.1 and at 10-months varied from 0 to 32.4, depending on the site.

Table XVII. Mean Change in WRS at 4-Month Follow-Up.

Follow-up	Unadjusted Mean ± SE (95% CI)
4 Months	21.7 ± 4.2 (13.3, 30.1)
10 Months	19.8 ± 4.3 (11.1, 28.4)

Table XVIII. Word Recognition Score at 4-Months Compared to Baseline.

	Site 103 N (%)	Site 105 N (%)	Site 109 N (%)
Better HA	11 (52.4)	15 (83.3)	4 (26.7)
= HA	9 (42.9)	3 (16.7)	8 (53.3)
Below HA	1 (4.8)	0 (0.0)	3 (20.0)

Overall, 93% of Esteem® recipients scored equal to or better than their pre-implant hearing aid. A summary of the WRS data found in Tables XVI and XVIII follows:

- 7% scored less than their pre-implant hearing aid (0%-20% depending upon clinical site),
- 37% scored equal to their pre-implant hearing aid (17%-53% depending upon clinical site), and
- 56% scored better than their pre-implant hearing aid (27%-83% depending upon clinical site).

Secondary Effectiveness Endpoint Analysis
Pure Tone Average (PTA)
The objective was to demonstrate that the Esteem System at the 4-month postactivation visit improves the 3-frequency (500, 1000, and 2000 Hz) pure tone average (PTA) when compared to the baseline unaided condition. For each subject, the 4-month, as well as the 10-month, air conduction data were compared to the baseline unaided data at various frequencies (Hz).

Table XIX details the mean air conduction change and the number of subjects in each functional "benefit" group at each frequency. The data is also plotted in Figure 10. There were 96% (52/54) of subjects at the 4-month interval and 92% (48/52) at the 10-month interval who had PTA change greater than 10 dB.

Table XIX. Air Conduction Threshold Change at 4 and 10 Months.

	Air Conduction Thresholds 4 Months N=54								
	250	500	1000	2000	3000	4000	6000	8000	PTA
Mean delta from Baseline ± SE (CI range)	12 ± 2 (16, 8)	19 ± 2 (22, 16)	26 ± 2 (30, 23)	35 ± 2 (39, 32)	23 ± 2 (27, 19)	17 ± 2 (21, 12)	8 ± 2 (12, 4)	0 ± 2 (5, -5)	27 ± 1 (30, 24)
% Greater than +10 dB	25/54 (46%)	38/54 (70%)	49/54 (91%)	51/54 (94%)	44/54 (81%)	35/54 (65%)	23/54 (43%)	8/54 (15%)	52/54 (96%)
% Stable (±10 dB)	28/54 (52%)	16/54 (30%)	5/54 (9%)	3/54 (6%)	8/54 (15%)	16/54 (30%)	20/54 (37%)	23/54 (43%)	2/54 (4%)
% Less than -10 dB	1/54 (2%)	0/54 (0%)	0/54 (0%)	0/54 (0%)	1/54 (2%)	2/54 (4%)	6/54 (11%)	7/54 (13%)	0/54 (0%)
% No Response	0/54 (0%)	0/54 (0%)	0/54 (0%)	0/54 (0%)	1/54 (2%)	1/54 (2%)	5/54 (9%)	16/54 (30%)	0/54 (0%)

	Air Conduction Thresholds 10 Months N=52								
	250	500	1000	2000	3000	4000	6000	8000	PTA
Mean delta from Baseline ± SE (CI range)	11 ± 2 (15, 8)	20 ± 1 (23, 17)	27 ± 2 (30, 23)	36 ± 2 (40, 33)	26 ± 2 (30, 22)	18 ± 2 (22, 14)	10 ± 2 (15, 5)	1 ± 3 (6, -5)	27 ± 1 (30, 25)
% Greater than +10 dB	23/52 (44%)	40/52 (77%)	46/52 (88%)	49/52 (94%)	43/52 (83%)	35/52 (67%)	25/52 (48%)	10/52 (19%)	48/52 (92%)
% Stable (±10 dB)	29/52 (56%)	12/52 (23%)	5/52 (10%)	3/52 (6%)	6/52 (12%)	13/52 (25%)	16/52 (31%)	20/52 (38%)	4/52 (8%)
% Less than -10 dB	0/52 (0%)	0/52 (0%)	1/52 (2%)	0/52 (0%)	1/52 (2%)	3/52 (6%)	6/52 (12%)	6/52 (12%)	0/52 (0%)
% No Response	0/52 (0%)	0/52 (0%)	0/52 (0%)	0/52 (0%)	2/52 (4%)	1/52 (2%)	5/52 (10%)	16/52 (31%)	0/52 (0%)

The denominator of 54 includes those who had "No Response." There were 5/54 (9%) and 16/54 (30%) "No Response" for 6000 and 8000 Hz, respectively. "No Response" for 6000 and 8000 Hz would not affect PTA

The mean PTA change at the 4-month from the baseline was 27 dB (SD=11). There were 52 out of 54 subjects who had PTA change greater than 10 dB, two subjects within ± 10 dB, and no subject below 10 dB.

QuickSIN

The objective was to demonstrate that the Esteem System at the 4-months postactivation visit is as effective as or better than the hearing aid for improving speech discrimination (intelligibility) as shown by the QuickSIN (speech in noise) test results.

The change with the Esteem® System from the aided baseline was -1 ± 1 at 4-month and 0 ± 0 at 10-month follow-up. The QuickSIN Test Manual quantifies the amount of SNR Loss (in dB) in relation to the degree (category) of SNR loss. Based on the cutoff values specified in QuickSIN Test Manual, the distributions of SNR Loss for the baseline aided and unaided conditions as well as for the 4- and 10-month intervals are provided in Table XX. The distributions of SNR loss at baseline aided condition and at the 4 and 10 month visits were comparable.

Table XX. QuickSIN SNR Loss Distributions.

SNR Loss	Degree of SNR Loss	Baseline Unaided (N=57)	Baseline Aided (N=57)	4 Month (N=54)	10 Month (N=52)
0-3 dB	Normal/near normal	2 (4%)	1 (2%)	1 (2%)	1 (2%)
>3-7 dB	Mild	12 (21%)	10 (18%)	8 (15%)	10 (19%)
>7-15 dB	Moderate	19 (33%)	29 (51%)	24 (44%)	29 (56%)
>15 dB	Severe	24 (42%)	17 (30%)	20 (37%)	12 (23%)

APHAB Quality of Life (QOL)

The objective was to show that the Esteem® System improves Quality-of-Life when compared to the baseline aided condition as shown by APHAB scores (time period not specified in the clinical protocol). The mean benefit scores over the unaided condition were collected for the pre-implant baseline aided condition and at the 4- and 10-month intervals as shown in Table XXI. The APHAB score is broken down into sub-categories of Easy Communication Situations (EC), Background Noise Situations (BN), Reverberate Environments (RV) and Aversiveness (AV).

As shown in Table XXI, there was a mean increase of 10.9 (standard deviation = 17.9) in benefit score (APHAB) at 4-month comparing to the baseline (pre-implant aided condition). The mean change in the four subscales ranged from 8.4 to 13.5, with the Easy Communication Situations (EC) subscale having the largest increase and the Reverberate Environment (RV) subscale having the smallest increase.

Table XXI. APHAB Mean Benefit Score (mean +/- standard error).

	Global Score mean ± se n (95% CI)	EC Scale mean ± se n (95% CI)	BN Scale mean ± se n (95% CI)	RV Scale mean ± se n (95% CI)	AV Scale mean ± se n (95% CI)
Baseline Aided	18.7±1.7 59 (15.4, 22.0)	38.9±2.9 59 (33.1, 44.7)	29.8±2.2 59 (25.4, 34.3)	34.7±2.6 59 (29.6, 39.9)	-28.9±2.9 59 (-34.8, -23.0)
Esteem 4-Month	28.3±2.5 53 (23.3, 33.3)	50.5±3.1 53 (44.3, 56.7)	39.5±3.3 53 (32.8, 46.2)	42.0±3.5 53 (35.0, 49.0)	-19.0±3.8 53 (-26.6, -11.4)
Mean Difference in Benefit Score	10.9±2.5 53 (5.9, 15.8)	13.5±3.2 53 (7.1, 20.0)	10.2±3.1 53 (4.1, 16.3)	8.4±3.1 53 (2.1, 14.6)	11.4±4.0 53 (3.3, 19.5)
Esteem 10-Month	26.3±2.8 51 (20.7, 31.8)	48.1±3.4 51 (41.2, 55.0)	36.0±3.6 51 (28.7, 43.3)	38.5±3.9 51 (30.6, 46.4)	-17.9±3.9 51 (-25.7, -10.2)
Mean Difference in Benefit Score	8.9±2.6 51 (3.8, 14.1)	11.4±3.4 51 (4.5, 18.3)	7.1±3.2 51 (0.7, 13.4)	5.0±3.1 51 (-1.3, 11.3)	12.2±4.0 51 (4.1, 20.2)

Table XXII provides the individual subject APHAB scores in percentage steps for Esteem at 4-months and 10-months follow-up compared to pre-implant baseline aided condition. The number and percent of subjects meeting each comparison step are provided for each APHAB score.

Table XXII. APHAB Comparison by Subject.

	4 Month APHAB Comparison Results N=53				
	Total	EC	BN	RV	AV
% Better HA > +22%	13/53 (25%)	15/53 (28%)	18/53 (34%)	14/53 (26%)	17/53 (32%)
% Better HA +10 to 21%	14/53 (26%)	12/53 (23%)	10/53 (19%)	9/53 (17%)	11/53 (21%)
% Better HA +5 to 9%	5/53 (9%)	10/53 (19%)	4/53 (8%)	5/53 (9%)	4/53 (8%)
% Equal HA (±4%)	11/53 (21%)	6/53 (11%)	7/53 (13%)	9/53 (17%)	9/53 (17%)
% Below HA -5 to -9%	3/53 (6%)	1/53 (2%)	7/53 (13%)	6/53 (11%)	1/53 (2%)
% Below HA -10 to -21%	4/53 (8%)	6/53 (11%)	4/53 (8%)	8/53 (15%)	4/53 (8%)
% Below HA < -22%	3/53 (6%)	3/53 (6%)	3/53 (6%)	2/53 (4%)	7/53 (13%)

	10 Month APHAB Comparison Results N=51				
	Total	EC	BN	RV	AV
% Better HA > +22%	9/51 (18%)	13/51 (25%)	13/51 (25%)	11/51 (22%)	16/51 (31%)
% Better HA +10 to 21%	16/51 (31%)	16/51 (31%)	10/51 (20%)	13/51 (25%)	11/51 (22%)
% Better HA +5 to 9%	7/51 (14%)	6/51 (12%)	3/51 (6%)	1/51 (2%)	3/51 (6%)
% Equal HA (±4%)	8/51 (16%)	8/51 (16%)	10/51 (20%)	8/51 (16%)	7/51 (14%)
% Below HA -5 to -9%	6/51 (12%)	3/51 (6%)	5/51 (10%)	5/51 (10%)	5/51 (10%)
% Below HA -10 to -21%	2/51 (4%)	3/51 (6%)	6/51 (12%)	9/51 (18%)	7/51 (14%)
% Below HA < -22%	3/51 (6%)	2/51 (4%)	4/51 (8%)	4/51 (8%)	2/51 (4%)

As for the individual benefit comparison, according to the *Instructions for Manual Scoring of the APHAB*, a significant benefit has occurred if a difference of ≥ 22% is obtained for the EC, RV or BN score. If all three scores improve by ≥ 10%, there is a 96% probability that a true benefit has occurred. If all three scores improve by ≥ 5%, there is an 89% probability that a true benefit has occurred. Scoring of the benefit scores for the baseline aided condition and the Esteem at 4 and 10-month follow-up was calculated versus baseline unaided condition. In addition, the Esteem at the 4 and 10-month evaluation was compared to the baseline aided condition for each subject according to these same criteria. The number of subjects meeting each of the above scoring criteria is presented in Table XXIII.

There were 25 subjects (47%) at 4-month follow-up and 21 subjects (41%) at 10-month follow-up who had a greater than 22% improvement in EC, RV or BN. However, less than one in three showed 96% probability of a significant benefit according to the APHAB scoring guideline.

Table XXIII. APHAB – Benefit Categories.

Benefit Categories	Esteem vs Hearing Aid n/N (%) 4-Month	Esteem vs Hearing Aid n/N (%) 10-Month
Significant Benefit Subjects with a ≥ 22% improvement in EC, RV, or BN	25/53 (47.2%)	21/51 (41.2%)
96% Probability of a Significant Benefit Subjects with a ≥ 10% improvement in EC, RV, and BN	16/53 (30.2%)	13/51 (25.5%)
89% Probability of a Significant Benefit Subjects with a ≥ 5% improvement in EC, RV, and BN	23/53 (43.4%)	19/51 (37.3%)

Esteem Questionnaire Quality of Life (QOL)

The objective was to gather subject's feedback and comments on the use of the Esteem® System relative to the baseline aided condition as shown by the Esteem Questionnaire (time period not specified in the protocol). At the 4- and 10-month follow-up, subjects completed a questionnaire rating various subjective attributes concerning their experience with the Esteem® System as compared to the baseline aided condition. Ratings were on a scale of 1 to 5, where 1 is much worse, 2 is somewhat worse, 3 is about the same, 4 is somewhat better, and 5 is much better.

The questions and responses are provided in Table XXIV. Subject ratings are summarized below:

- Clarity of Sound: 78% somewhat or much better, 7% equal, 15% somewhat or much worse
- Ability to Understand Speech in Background Noise: 69% somewhat or much better, 13% equal, and 18% somewhat or much worse
- Natural Sounding Voices: 76% somewhat or much better, 11% equal, 13% somewhat or much worse
- Understanding Conversation: 72% somewhat or much better, 17% equal, 11% somewhat or much worse
- Activity Level: 85% somewhat or much better, 11% equal, 4% somewhat or much worse
- Feeling of Confidence: 84% somewhat or much better, 8% equal, 8% somewhat or much worse
- Benefit of Invisibility: 66% somewhat or much better, 17% equal, 17% somewhat or much worse

Table XXIV. Esteem Questionnaire (Quality of Life).

Question	4 Month Response				
	1	2	3	4	5
How do you rate the clarity of the sound you hear with the *Esteem* compared to your hearing aid?	3/54 (6%)	5/54 (9%)	4/54 (7%)	13/54 (24%)	29/54 (54%)
How do you rate your ability to understand speech in background noise or street noise with the *Esteem* as compared to your hearing aid?	3/54 (6%)	7/54 (13%)	7/54 (13%)	17/54 (31%)	20/54 (37%)
How natural sounding are voices and other sounds compared to your hearing aid?	1/54 (2%)	6/54 (11%)	6/54 (11%)	13/54 (24%)	28/54 (52%)
How do you rate the benefit of the entire system being invisible to the onlooker compared to your hearing aid?	9/54 (17%)	0/54 (0%)	9/54 (17%)	12/54 (22%)	24/54 (44%)
How well do you understand conversation with your *Esteem* even when several people are talking compared to your hearing aid?	3/54 (6%)	3/54 (6%)	9/54 (17%)	18/54 (33%)	21/54 (39%)
How confident do you feel with the *Esteem* compared to your hearing aid?	2/53 (4%)	2/53 (4%)	4/53 (8%)	13/53 (25%)	32/53 (60%)
Does the Esteem allow you to live a more active lifestyle?	1/54 (2%)	1/54 (2%)	6/54 (11%)	13/54 (24%)	33/54 (61%)

Question	10 Month Response				
	1	2	3	4	5
How do you rate the clarity of the sound you hear with the *Esteem* compared to your hearing aid?	3/52 (6%)	5/52 (10%)	3/52 (6%)	7/52 (13%)	34/52 (65%)
How do you rate your ability to understand speech in background noise or street noise with the *Esteem* as compared to your hearing aid?	5/52 (10%)	3/52 (6%)	7/52 (13%)	14/52 (27%)	23/52 (44%)
How natural sounding are voices and other sounds compared to your hearing aid?	3/52 (6%)	5/52 (10%)	4/52 (8%)	14/52 (27%)	26/52 (50%)
How do you rate the benefit of the entire system being invisible to the onlooker compared to your hearing aid?	5/52 (10%)	0/52 (0%)	11/52 (21%)	15/52 (29%)	21/52 (40%)
How well do you understand conversation with your *Esteem* even when several people are talking compared to your hearing aid?	3/52 (6%)	4/52 (8%)	10/52 (19%)	12/52 (23%)	23/52 (44%)
How confident do you feel with the *Esteem* compared to your hearing aid?	4/52 (8%)	3/52 (6%)	3/52 (6%)	12/52 (23%)	30/52 (58%)
Does the Esteem allow you to live a more active lifestyle?	1/52 (2%)	3/52 (6%)	3/52 (6%)	10/52 (19%)	35/52 (67%)

3. Subgroup Analyses

   Outcomes systematically stratified based on subjects' (a) age, (b) degree of hearing loss, (c) WRS, and (d) length of hearing aid use experience are shown in Table XXVI.

Table XXVI. Stratified Results.

Stratification Factor	Strata	N	SRT Change at 4 months		WRS Change at 4 months	
			Mean±SE	P-value For Strata Differences	Mean±SE	P-value For Strata Differences
Age	< 47 years	18	6.4±3.4	0.242	16.9±7.9	0.708
	47 - 60.3 years	18	13.1±3.4		25.2±8.1	
	> 60.3 years	18	12.5±2.2		23.0±5.8	
Baseline Hearing Loss Severity (PTA)	Mild	3	10.0±5.0	0.843	20.7±6.6	0.659
	Moderate	41	11.2±2.1		19.8±4.1	
	Severe	10	8.5±4.2		29.8±15.2	
Baseline unaided WRS (at max)	< 60%	10	15.0±5.3	0.389	22.4±8.5	0.300
	60% – 80%	23	11.1±2.4		28.4±7.1	
	> 80%	21	8.1±2.9		14.0±6.0	
Length of hearing aid experience	<8 years	18	10.6±2.3	0.232	17.6±4.1	0.399
	8 – 16 years	18	14.4±3.8		29.8±7.3	
	>16 years	18	6.9±2.9		17.8±9.3	

For age and length of hearing aid experience, subjects were divided into three equal sized groups (i.e. tertiles). For WRS, the division into three groups was based on commonly used clinical cutoff values of 60% and 80%.

Results were consistent among subgroups of subjects. Subjects of each subgroup exhibited a benefit of the Esteem System over the pre-implant aided condition.

However, the number of subjects for the mild hearing loss subgroup is only three, which makes it difficult to interpret results for this subgroup. Subsequently the mild hearing loss indication was removed from the labeling.

Although not statistically significant, the study device was shown to be more effective for females than for males. Mean SRT at 4 months for females was 14.7 (SD=14.4) vs 8.4 (SD=12.0) for males. Mean WRS at 4 months for females was 31.7 (SD=27.1) vs. 16.3 (SD=31.4) for males.

Section X / Appendix 1. Safety Algorithm

Background: Bone conduction (BC) using forehead probe placement was the primary test for cochlear function stability. While forehead placement would minimize some of the test variability issues associated with the mastoid probe placement as detailed in IDE G000321, it is still possible that BC test-retest variability may result in test results outside the ±10 dB limits due to equipment limitations and probe placement. As an improvement over the methods used in IDE G000321, the Safety Algorithm has been refined for use in this new clinical trial. In addition to bone conduction, the EnvoyGram function was used as an in-situ audiogram to directly stimulate the cochlea. This method would be more accurate and a better indicator of cochlear stability than the previous EnvoyGram tests where testing done at implant was used to predict future performance.

The EnvoyGram IT: In addition to the programmable parameters used to affect the incoming signal, the Sound Processor has an internal tone generator that can be accessed through the Esteem Programmer in a test mode called the EnvoyGram IT (EnvoyGram In-situ). In other words, the EnvoyGram IT is an in-situ audiogram utilizing the Driver to test cochlear function. When entering this test mode, the Sensor is deactivated. The Esteem Programmer software allows the audiologists to select a frequency in the range 250 to 4000 Hz and amplitude in the range 55 to 119 dB SPL. The Sound Processor synthesizes and delivers a pure tone signal to the Driver to induce known vibrations directly into the cochlea. There are twelve steps of amplitude. Each step provides a 4 - 6 dB increase over the previous step. The typical EnvoyGram IT levels are based on: (a) typical intact chain displacement of 40 nm at 100 dB for frequencies below 1 kHz (Validated per ASTM F 2504 and EMC 003798-001), (b) a typical Model 7502 Driver displacement in temporal bones of 88 nm/V (Validated per EMC 003798-001), and (c) a typical SP tone output for each volume and tone setting (Validated per EMC 003788-101 and EMC 003872-001).

Each patient's intact chain has a unique displacement profile. During implant of the Esteem, intact chain data is measured and recorded to provide a normalization factor for the EnvoyGram IT. Intra-operative data, ASTM F 2504, and temporal bone studies at Envoy (i.e. EMC 003798-001) all indicate that patient-to-patient variability of intact chain displacement is at least ±6 dB. ASTM F 2504 cites a 95% confidence interval of ±6 dB in temporal bones. Clinical experience has also shown that accurately quantifying the intact chain displacement of each patient in a live surgical field is also limited to approximately ±6 dB, due to presence of fluid in the middle ear space, available LDV laser angle, etc.

The EnvoyGram IT test protocol is similar to that of an audiogram. The intact-chain measurements are recorded on the Procedure and Discharge CRF (EMC 003900-003) and entered into the EnvoyGram IT by the audiologist. The test methodology is performed consistent with the Hughson-Westlake procedure. A signal is presented at the prescribed amplitude and frequency. If the subject acknowledges the signal, the intensity level is decreased two steps (10 - 12 dB). If that signal is not acknowledged, the intensity level is increased one step (6 dB), thus determining a threshold. This threshold provides a measure of cochlear function independent of the external auditory mechanism.

EnvoyGram IT SPL levels are customized to the patient by taking into account each patient's IC data. For instance, a patient with typical 40 nm IC displacement at 100 dB will have levels from 55 to 117 dB, but a patient with stiff 20 nm IC displacement at 100 dB will have levels from 61 to 123 dB. The table below lists the EnvoyGram levels for a) a typical intact chain displacement of 40 nm at 1.0 kHz, 100 dB SPL, b) an intact chain displacement of 20 nm at 1.0 kHz, 100 dB SPL, and c) an intact chain displacement of 80 nm at 1.0 kHz, 100 dB SPL. Table 1 displays the EnvoyGram IT levels in Esteem Programmer after intra-operative IC data entry. EnvoyGram IT levels are listed in dB SPL and are automatically calculated in the Esteem Programmer for each patient's IC data collected during implant procedure. These are the levels available for each of the test frequencies.

Typical (40nm IC @ 100dB SPL)	55	58	64	70	75	80	87	94	100	106	111	119
Stiff (20nm IC @ 100dB SPL)	61	64	70	76	81	86	93	100	106	112	117	125
Loose (80nm IC @ 100dB SPL)	49	52	58	64	69	74	81	88	94	100	105	113

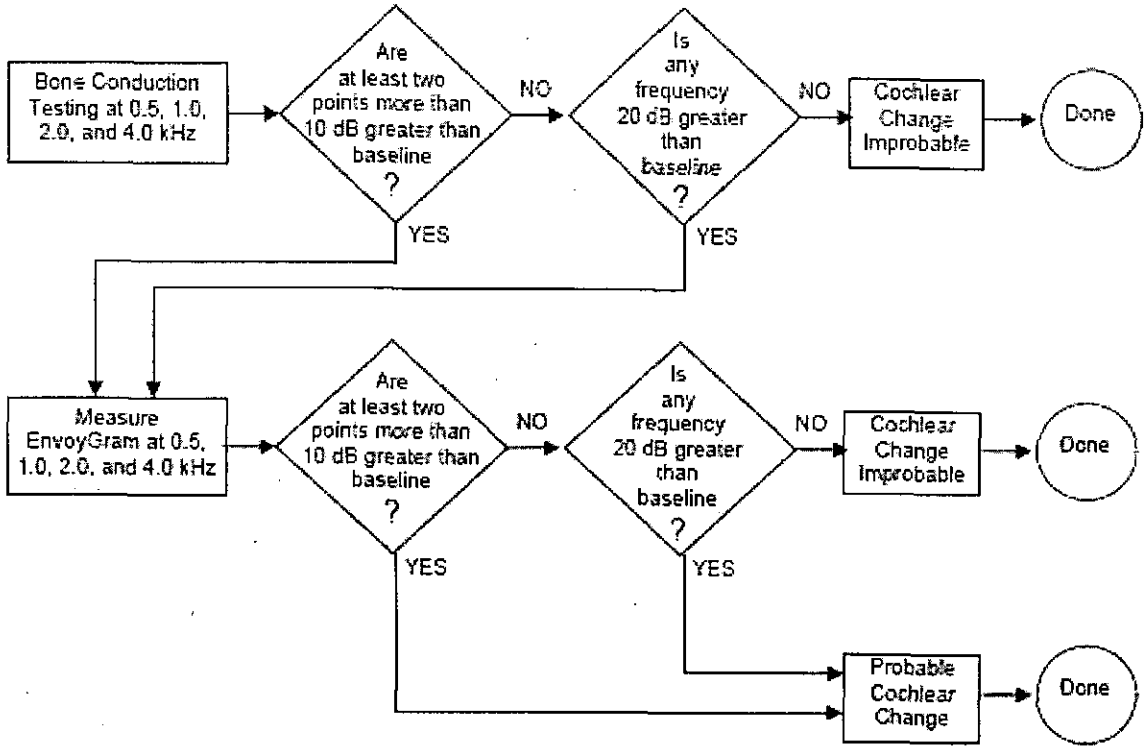
Since the EnvoyGram IT levels are calibrated to each patient, the "predicted" EnvoyGram IT thresholds are equal to the baseline pre-implant unaided audiogram for each test frequency. For instance, a patient with 55 dB baseline air conduction threshold at 1 kHz and 80 nm measured IC would have a predicted EnvoyGram IT of 58 dB at 1 kHz (first level above baseline unaided threshold of 55 dB).

Safety Algorithm Explanation. The first level of the safety algorithm will use standard bone conduction (BC) thresholds. Bone conduction thresholds are measured in the implanted ear at 0.5, 1.0, 2.0, and 4.0 kHz at baseline and follow-up visits. If less than two of the follow-up thresholds are more than 10 dB greater than the baseline thresholds, then the individual test frequencies are evaluated. At each test frequency, if the follow-up threshold is less than 20 dB greater than the baseline threshold then the algorithm is considered complete, with a conclusion that cochlear change is improbable. However, if at least two of the thresholds have increased more than 10 dB or if any individual threshold has increased by 20 dB or more, then the EnvoyGram data is evaluated.

The second level of the safety algorithm will use EnvoyGram thresholds. Baseline unaided air conduction pure tone thresholds at 0.5, 1.0, 2.0, and 4.0 kHz are measured at baseline. Similarly, EnvoyGram thresholds are measured in the implanted ear at 0.5, 1.0, 2.0, and 4.0 kHz at follow-up visits. Based on the intra-operative intact chain data, an EnvoyGram equivalent dB threshold is calculated for each of the four test frequencies. If less than two of the follow-up EnvoyGram thresholds are more than 10 dB greater than the baseline thresholds, then the individual test frequencies are evaluated. At each test frequency, if the follow-up EnvoyGram threshold is less than 20 dB greater than the baseline threshold then the algorithm is considered complete, with a conclusion that cochlear change is improbable. However, if at least two of the EnvoyGram thresholds have increased more than 10 dB or if any individual EnvoyGram threshold has increased by 20 dB or more, then the algorithm is considered complete with a conclusion that cochlear change is probable.

For patients with moderate to severe sensorineural hearing loss, non-responses (NR) are not uncommon during bone-conduction testing. If an NR occurs during baseline bone conduction testing, that test frequency is not evaluated (for the same patient) in the follow-up bone conduction portion of the safety algorithm. However, if an NR occurs during follow-up bone conduction testing (and is not preceded by a baseline NR at the same test frequency), the corresponding EnvoyGram threshold change from baseline is substituted at the bone conduction NR test frequency.

Bone Conduction/Safety Algorithm



Section X / Appendix 2. Audiometric Data for Reconstructed Subjects

Subject 0203-103-17 JATST
IDE G000321
Incudoplasty-2 Year Post Reconstruction

		Pre-Implant Unaided	Pre-Reconstruction	Post Reconstruction
Air Conduction	500 Hz	55	NR	45
	1000 Hz	45	NR	45
	2000 Hz	50	NR	50
	3- Frequency Average (dB HL)	50	NR	47
SRT	(in dB)	45	NR	45
WRS (inserts)	Maximum	92	NR	72
Bone Conduction	500 Hz	50		45
	1000 Hz	40		45
	2000 Hz	50		60
	3000 Hz	60		60
	4000 HZ	60		70
	3- Frequency Average (dB HL)	47		50
Air-Bone Gap	500 Hz	5		0
	1000 Hz	5		0
	2000 Hz	0		-10
	3- Frequency Average (dB HL)	3		-3

NR=No Response

Subject 0203-104-06 KAMHA
IDE G000321
Incudoplasty-2 Months Post Reconstruction

		Pre-Implant Unaided	Pre-Reconstruction	Post Reconstruction
Air Conduction	500 Hz	40	90	45
	1000 Hz	45	85	50
	2000 Hz	55	70	50
	3- Frequency Average (dB HL)	47	82	48
SRT	(in dB)	45	90	40
Speech Disc	Maximum	100	64	76
Bone Conduction	500 Hz	45		35
	1000 Hz	50		45
	2000 Hz	60		40
	3000 Hz	55		65
	4000 HZ	50		70
	3- Frequency Average (dB HL)	52		40
Air-Bone Gap	500 Hz	-5		10
	1000 Hz	-5		5
	2000 Hz	-5		10
	3- Frequency Average (dB HL)	-5		8

Subject 0203-102-05 KAGNI
IDE G000321
PORP-9 Months Post Reconstruction

		Pre-Implant Unaided	Pre-Reconstruction	Post Reconstruction
Air Conduction	500 Hz	40	NA	60
	1000 Hz	50	NA	70
	2000 Hz	60	NA	65
	3- Frequency Average (dB HL)	50	NA	65
SRT	(in dB)	45	NA	60
Speech Disc	Maximum	92	NA	80
Bone Conduction	500 Hz	30		55
	1000 Hz	40		65
	2000 Hz	65		60
	3000 Hz	65		NA
	4000 HZ	65		80
	3- Frequency Average (dB HL)	44		60
Air-Bone Gap	500 Hz	10		5
	1000 Hz	10		5
	2000 Hz	-5		5
	3- Frequency Average (dB HL)	1		5

NA = Not Available

Subject 0204-105-37
IDE G070162
Incudoplasty-12 Weeks Post Reconstruction

		Pre-Implant Unaided	Pre-Reconstruction	Post Reconstruction
Air Conduction	500 Hz	55	NA	60
	1000 Hz	60	NA	60
	2000 Hz	55	NA	55
	3- Frequency Average (dB HL)	57	NA	58
SRT	(in dB)	55	NA	60
WRS (inserts)	Maximum	100	NA	100
Bone Conduction	500 Hz	40		40
	1000 Hz	55		40
	2000 Hz	55		45
	3000 Hz	65		55
	4000 HZ	65		75
	3- Frequency Average (dB HL)	50		42
Air-Bone Gap	500 Hz	15		20
	1000 Hz	5		20
	2000 Hz	0		10
	3- Frequency Average (dB HL)	7		16

NA=Not Available; Reconstruction was done at the same time as explant.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The clinical information is discussed in Section X.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

A meeting of the Ear, Nose, and Throat Devices Advisory Panel was held on December 18, 2009, to discuss and provide recommendations to FDA regarding the clinical data presented in the Pre-Market Approval Application (P090018) for the Esteem Totally Implantable Hearing System sponsored by Envoy Medical Corporation. The Esteem® is a totally implantable hearing device that is implanted in the middle ear to help hearing in adults with sensorineural hearing loss by replicating the ossicular chain and providing additional gain.

The Panel heard the company and FDA presentations, discussed the clinical data presented, addressed the FDA questions, and finally voted unanimously (15-0) to recommend that the PMA application for the Esteem Totally Implantable Hearing System

sponsored by Envoy Medical Corporation be found "Approvable with Conditions." The proposed conditions included:

1) modification of the "Indications for Use" statement to specify only bilateral moderate to severe, sensorineural hearing loss;

2) patient speech intelligibility assessment must use recorded stimuli;

3) a minimum one-month trial with a hearing aid prior to acceptance for device implantation to ensure prior experience with traditional, acoustic hearing aid;

4) labeling should include performance results from the pivotal clinical trial, noting limitations of effectiveness data (Speech Reception Threshold, Word Recognition Score) compared to traditional acoustic hearing aid;

5) subject information should include reporting all adverse events;

6) a rigorous training and certification program must be completed by treating surgeons and audiologists prior to device usage; and

7) a post-approval study is necessary for following current subjects and to track new patients.

The webpage link to the P090018 panel transcript is found at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/EarNoseandThroatDevicesPanel/ucm146740.htm

B. FDA's Post-Panel Action

Both FDA and the applicant accepted all of the panel recommendations. Following the panel meeting, the applicant adequately revised the labeling to reflect all conditions of approval recommended by the panel. The applicant continued to work with FDA to adequately revise the post-approval study design in the 30 days following issuance of the approval order.

During the December 18, 2009 panel meeting, the panel members unanimously voted (15-0) in favor of a conditional approval for the Esteem® System. Conditions applicable to the safety of the device included:

1. Panel members recommended that "Normal Tympanic Membrane" to be added to the Indications for Use statement in addition Inclusion Criteria requirement.

2. Intense training would be provided to select group of surgeons (neuro-otologists) to overcome the site variability in the occurrence of adverse events.

3. 7% incidence of facial paresis/paralysis was a concern for all participants. Panel recommended better training of surgeons in proper surgical technique for the

Esteem Device placement to overcome this high incidence of facial nerve adverse event.

4. Improve labeling to accurately reflect the incidence of adverse events, revision rates, explantation rates, and extent of surgical procedures.

Subsequent to the ENT Advisory Panel recommendations, the applicant satisfactorily modified all pertinent documents to accurately reflect the incidence of revision surgeries, explantations, and facial nerve adverse events.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

The primary safety objectives included: (a) incidence of serious adverse device effects (SADE), (b) incidence of device failures and replacements, (c) bone conduction (BC) threshold at 4 months post-activation vs. pre-implant, and (d) safety algorithm (SA) for those that fail BC. A summary of the results is shown below.

a. Incidence of SADEs:

- Three (3) subjects experienced facial weakness / incision issues.
- Three (3) subjects required revision procedures to date.
- The SADE rate was 10.5% (6 of 57).

In addition, major adverse event rates included:

- Taste Disturbance: 42% of patients (14% ongoing after 1 year).
- Facial Paresis/Paralysis: 7% of patients (1% ongoing after 1 year).
- Tinnitus: 18% (5% ongoing after 1 yr.)

b. Incidence device failures:

- Three (3) failures resulting in approved revisions were reported in three unique subjects prior to the 4-month follow-up.
- The failure rate was 5.3% (3 of 57).

c. Bone conduction threshold:

- Average 3 frequency (500, 1K, 2K) bone conduction change of 0.1 dB at 4 months vs. pre-implant.
- Average 3 frequency (500, 1K, 2K) bone conduction change of -0.8 dB at 10

months vs. pre-implant.

d. safety algorithm (SA) for those that fail BC

- Individually, no subjects (0) at 4 months had BC/SA change per the protocol criteria from pre-implant.
- Individually, one subject (1) at 10 months had BC/SA change per the protocol criteria from pre-implant at 4 kHz.

B. Effectiveness Conclusions

The primary effectiveness endpoints included: (a) Speech Reception Threshold (SRT) at 4 months post-activation vs. pre-implanted aided condition and (b) Word Recognition Score (WRS) at 4 months post-activation vs. pre-implanted aided condition (at 50 dB HL input condition).

a. Speech Reception Threshold (SRT):

- Average SRT improvement of 10.6 dB at 4 months compared to their baseline aided condition (95% confidence interval varied from 7.1 to 14.2). The heterogeneity in the treatment effect among sites is statistically significant (p-value < 0.01). Due to site variability, the range of mean improvement was 1.3-16.9 dB.
- Average SRT improvement of 11.4 dB at 10 months compared to their baseline aided condition.

b. Word Recognition Score (WRS):

At 4 months:

- Average WRS improvement at 4 months was 21.7 (95% Confidence Interval: 13.3 to 30.1).
- WRS was the same or better in 93% and worse in 7% of subjects as compared to hearing aids.

There is statistically significant heterogeneity in WRS among the sites (p-value = 0.01).

- 7% scored less than their pre-implant hearing aid (0%-20% depending upon clinical site),
- 37% scored equal to their pre-implant hearing aid (17%-53% depending upon clinical site), and
- 56% scored better than their pre-implant hearing aid (27%-83% depending upon clinical site).

At 10 months:

- Average WRS improvement at 10 months was 19.8 (95% confidence interval: 11.1 to 28.4).
- WRS was the same or better in 88% and worse in 12% of subjects as compared to hearing aids.

Regarding the primary effectiveness data summarized above, the panel recommended that the applicant can claim that the Esteem can perform as well as hearing aids. However, the panel recommended disallowing any labeling claims that the Esteem is superior to hearing aids.

C. ***Overall Conclusions***

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The panel voted unanimously (15-0) for approval with conditions. These conditions were adequately addressed by the sponsor prior to issuance of the approval order.

XIV. CDRH DECISION

FDA issued an approval order on March 17, 2010.

The final conditions of approval cited in the approval order are described below.

1. *Extended Follow-up of Premarket Cohort Study*: Per agreement dated January 27, 2010 (e-mail) this study will address the following question: What is the long-term (5 years) safety and effectiveness of the Esteem device? This question will be addressed by extending the follow-up of the PMA pivotal clinical trial, which was designed as a prospective, multi-center non-randomized, 1-arm clinical trial to evaluate the safety and effectiveness of the Esteem® device. For this trial the subject acts as his or her own control. A total of 61 out of 62 patients were enrolled in the PMA pivotal clinical trial and followed out to one year. The continued access expansion study will follow these subjects out to 5-year follow-up. The study endpoints include: speech reception threshold (SRT) and word recognition score (WRS) for effectiveness; and safety endpoints include all adverse events at each follow up visit. The study protocol will include specific statistical hypotheses for the effectiveness endpoint at 5-years.

2. *The New Enrollment Study*: Per agreement dated January 27, 2010 (e-mail) this study will address the following questions: What is the long-term (5 years) safety and effectiveness of the Esteem device? Is the incidence of facial pareses/paralyses greater than 7% at 1-month? These questions will be addressed in a prospective, multi-center, non-randomized, audiologist-blinded, 1-arm observational study. For this study the subject acts as his or her own control. A total of 120 newly enrolled patients treated by newly trained surgeons at up to 10 investigational sites; consecutively treated patients

will be invited to participate in this post-approval study. The study participants will be followed for 5-years. Study endpoints for effectiveness include speech reception threshold (SRT) and word recognition score (WRS). Study endpoints for safety include all adverse events at each follow up visit. A safety hypothesis will be performed at 1-month (facial paresis/paralysis). An effectiveness hypothesis will be performed at 5 years.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.
Post-approval Requirements and Restrictions: See approval order.